Clinical Case Reports International

Case Report
Published: 01 Aug, 2022

Anti-Angiogenic Therapy-Related Proteinuria in a Patient with Advanced Pancreatic Cancer: A Case Report and Review of the Literature

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Abstract

Along with the widely use of anti-angiogenic therapies, recognition of the anti-VEGF related renal injury has increased. However, renal biopsy is rarely available in cancer patients who underwent systemic treatment; therefore, the renal consequences caused by inhibition of VEGF are usually underestimated. In here, we report a case of pancreatic cancer patient who developed proteinuria under the treatment of bevacizumab. The efficacy and side effects of bevacizumab were reported, and the mechanism of proteinuria and the principle of treatment were explored.

Introduction

More than 15 years ago, anti-angiogenic therapy firstly entered clinical practice, marking the new edge of anti-cancer treatment. The representative drug is bevacizumab, a VEGF-A targeting monoclonal antibody. Combining with chemotherapies, it has been widely used in oncology therapeutic areas with eight approved indications across different types of solid tumors, including Non-Small-Cell Lung Cancer (NSCLC), Metastatic Colorectal Cancer (mCRC), Glioblastoma (GBM), Renal Cell Carcinoma (RCC), Ovarian Cancer (OC) and cervical cancer [1].

However, bevacizumab has also shown efficacy in other types of solid tumors, for example, pancreatic cancer, which has very poor prognosis and causes huge disease burden for patients due to the limited options of treatment. Cutting edge researches consistently show that angiogenesis is the prerequisite for invasive tumor growth and distant metastasis. Therefore, anti-angiogenic drugs are valuable options for treatment of pancreatic cancer [2].

Several clinical trials have shown the efficacy of bevacizumab in patients with pancreatic cancer. In a phase II clinical study, bevacizumab combined with gemcitabine in the treatment of advanced pancreatic cancer achieved an objective effective rate of 21% and a disease control rate of 46%, with median PFS 5.7 months and a median OS 8.8 months [3]. Similarly, a phase III trial also demonstrates that combining bevacizumab with gemcitabine significantly improved PFS in patients with metastatic pancreatic cancer (HR, 0.73; 95% CI, 0.61 to 0.86; P=0.0002) [4].

Due to the unique mechanism of inhibiting VEGF, bevacizumab has many adverse effects, including hypertension, proteinuria, bleeding, thrombosis, gastrointestinal perforation, and congestive heart failure, etc. Among them, proteinuria and hypertension are the second most common adverse effects after bleeding, and are often considered as dose limiting toxicity [5].

Considering the high incidence of proteinuria and its damage for kidney, it is urgent for clinician to notice this bevacizumab-related proteinuria.

Case Presentation

A 56-year-old female patient had a medical history of hypertension for more than 18 years, with a maximum blood pressure reading of 185/105 mmHg. Blood pressure was controlled with compound-reserpine-triamterene tablets. In March 2019, the patient underwent duodenum-preserving pancreatic head resection due to the discovery of a pancreatic head mass, and postoperative pathology revealed poorly-differentiated adenocarcinoma of the pancreas, invasion of the common bile duct, and no lymph node metastases. After surgery, 6 cycles of adjuvant chemotherapy with capecitabine were performed (March 2019 to September 2019). In March 2020, examination showed elevated serum carbohydrate antigen 19-9 (CA19-9) >1000 U/mL; PET-CT demonstrated the following: Abnormal increased metabolic signals in the region of the first

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Received Date: *12 Jul 2022*
Accepted Date: *27 Jul 2022*
Published Date: *01 Aug 2022*

Citation:
Ma K, Zhang Y. Anti-Angiogenic Therapy-Related Proteinuria in a Patient with Advanced Pancreatic Cancer: A Case Report and Review of the Literature. Clin Case Rep Int. 2022; 6: 1364.

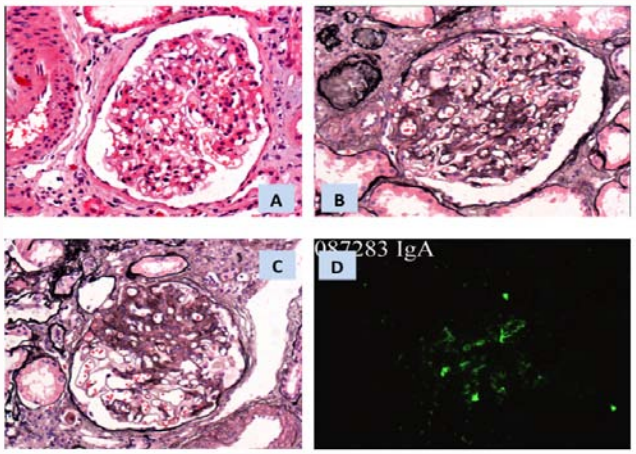

Figure 1: Renal biopsy pathology revealed proliferative glomerulonephritis (moderate) with segmental sclerosis, which was consistent with IgA nephropathy grade III considering together the findings of immunohistochemistry.
A): HE staining showing cell proliferation; B): PASM staining showing glomerular cell proliferation; C): PASM staining showing focal glomerulosclerosis; and D): immunofluorescence showing IgA +.

thoracic vertebra and left acetabulum, which were considered bone metastases; pulmonary nodules with high metabolic activity in both lungs, indicating the possibility of tumor metastases; multiple areas of increased radioactive uptake in the upper abdomen, hypermetabolic activity involving the right mediastinal-hilar lymph nodes, and pleural effusion. Considering the disease progression, erlotinib combined with gemcitabine was initiated then discontinued after 7 days (due to systemic pruritic rash). Subsequently, the patient was given 6 cycles of first-line chemotherapy with gemcitabine 1.4 mg d1, d8 + carboplatin 300 mg d1 + bevacizumab 600 mg d2 (21-day cycles) from March 2020 to August 2020. After 6 cycles of treatment, disease assessment revealed stable disease. Bevacizumab 600 mg d1 (21-day cycle) maintenance therapy was performed for 2 cycles from August 2020 to November 2020. During treatment, the patient had intermittent epitasis and grade I–II myelosuppression. In April 2020, routine urinalysis showed trace urinary protein and erythrocytes 90/μL. The patient reported intermittent foamy urine that became more noticeable over time since July. In October, the patient developed hypertension with a maximum of 205/105 mmHg following bevacizumab administration, and the blood pressure was poorly controlled with compound-reserpine-triamterene tablets and metoprolol. Repeat urinalyses all revealed proteinuria, specific gravity 1.040, pH 6.5, white blood cells 108.3/μL, red blood cells 51.7/μL, poikilocytes 100%, and protein >3.5 g/L. 24-h urine protein quantification was 0.96 g to 2.07 g.

Due to persistent proteinuria, renal biopsy was performed under local anesthesia on December 2020. Pathology under light microscopy showed proliferative glomerulonephritis (moderate) with segmental glomerulosclerosis which, when considered together with immunohistochemistry findings, was consistent with IgA nephropathy grade III. Immunofluorescence: IgA+. Electron microscopy: consistent with proliferative glomerulonephritis (Figure 1). Therefore, following the initiation of nifedipine and losartan potassium tablets, the patient's proteinuria gradually turned negative and the hypertension was stable and well controlled. A repeat bone scan in December 2020 revealed bone metastases, and patients underwent subsequent treatment of second-line chemotherapy with pemetrexed + oxaliplatin. Urinalysis showed no definite proteinuria. The patient died from disease progression in March 2022.

Discussion

Advanced pancreatic cancer has the shortest life expectancy among solid tumors. Whether in developing or developed countries, the overall five-year survival rate is about 6% ranging from 2% to 9% [6]. Gemcitabine acts as the backbone of chemotherapy, with a response rate of only 5% and Overall Survival (OS) of 5.7 months when used alone. In addition, Gemcitabine combined with capecitabine, irinotecan or oxaliplatin, have also not showed survival advantages compared with single agent gemcitabine. Therefore, great expectations were placed on the combination of gemcitabine with novel drugs [7]. With the combination therapy of bevacizumab and gemcitabine, our patient experienced a prolonged PFS of the first-line regimen of 8.3 months, and OS was >24 months, which proved to be a remarkable survival benefit that is rarely seen in patients with advanced pancreatic cancer.

Unlike conventional cytotoxic chemotherapies, bevacizumab-related proteinuria and/or hypertension occurred in up to 20% to 30% of patients. The VEGF signaling pathway plays an important role in angiogenesis and maintenance of hemodynamic function. VEGF is expressed on glomerular podocytes, while its receptors are present on glomerular endothelial cells; VEGF expression is also important for maintaining glomerular structure and function, and either overexpression or down-regulation of VEGF may cause glomerular disease.

According to previous studies, proteinuria and/or hypertension associated with bevacizumab have the following characteristics: firstly, bevacizumab-induced proteinuria is dose dependent, with higher doses being associated with a higher incidence of proteinuria [8]. Secondly, the severity of proteinuria does not necessarily reflect the severity of renal pathological damage; many patients with Thrombotic Microangiopathy (TMA) as the only sign of nephropathy may also have grade I–II proteinuria [9]. In addition, animal models have suggested that renal damage caused by bevacizumab is related to high dosages, but there is no definite correlation between the severity of renal pathological changes and the severity of proteinuria associated with bevacizumab [10].

Renal biopsy pathology is the most critical tool for diagnosing bevacizumab-induced renal injury and prognosis. A review of previous studies of VEGF-related renal injury showed that, of 15 cases with renal biopsy pathology findings, 9 revealed TMA, 24-h proteinuria ranged from 0.16 g/24 h to 5.3 g/24 h, and other pathological changes including collapsing-like focal segmental glomerulosclerosis (cFSGS; 2 cases), proliferative glomerulonephritis, immune complex glomerulonephritis, IgA nephropathy, and crescentic glomerulonephritis [11]. In the largest-scale pathological analysis from an 8-year observational study of VEGF antibody-induced renal injury, 100 patients with proteinuria and/or hypertension/renal insufficiency underwent renal biopsy at 6.87 ± 7.18 months after treatment initiation. Anti-VEGF medications included VEGF mAb and VEGF tyrosine kinase inhibitors. Seventy-three of these patients presented with renal TMA, and the remaining 27 patients had various glomerulopathies, mainly minimal-change disease (MCN) and/or FSGS. Renal injury caused by bevacizumab was primarily TMA, with only 1 FSGS reported. Both proteinuria and hypertension recovered after bevacizumab discontinuation and initiation of antihypertensive drugs, and there were no patients with severe renal failure requiring

dialysis, suggesting that glomerular lesions caused by VEGF-targeted drugs are common with the main pathological changes being TMA and MCN/cFSGS, but with an overall favorable prognosis [12]. Therefore, careful risk assessment at an individual level is helpful to identify renal injury and determine appropriate management. In addition, the severity of proteinuria does not always mirror the severity of renal pathological changes, so it is essential to consider renal biopsy in patients with persistent proteinuria.

In this case report, proteinuria (graded 1 to 2 according to Common Terminology Criteria for Adverse Events [CTCAE] version 5.0 classification) occurred after more than 6 months of bevacizumab treatment and lasted for more than 1 month. The proteinuria did not resolve immediately after bevacizumab discontinuation. Hypertension, which was emergent during bevacizumab treatment, was refractory. Therefore, renal biopsy was performed. Pathology suggested proliferative glomerulonephritis, IgA nephropathy and benign sclerosis, without severe pathological changes such as TMA. After medical intervention with Angiotensin-Converting-Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs), the patient's hypertension was well controlled and stable, and the proteinuria gradually became negative and did not recur after further chemotherapy. The outcome was consistent with pathological changes of the kidney, avoiding the implementation of overtreatment or delayed anticancer therapy and without affecting the prognosis.

In summary, bevacizumab-related proteinuria is not necessarily a dose-limiting toxicity. It is important to periodically monitor renal function, routine urinalysis, and blood pressure during treatment, and to proactively control blood pressure within the normal range. For patients with persistent proteinuria, renal biopsy upon discontinuing the drug is safe and reliable, which is helpful in determining the prognosis and choosing further therapeutic drugs. For patients who have benign glomerular lesions as the main feature, ACEIs and ARBs can be selected to control hypertension and reduce proteinuria.

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