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Original contribution

Clinicopathological spectrum of kidney diseases in cancer patients treated with vascular endothelial growth factor inhibitors: a report of 5 cases and review of literature☆

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Summary Recently, cancer therapies have been supplemented by vascular endothelial growth factor (VEGF) inhibitors as anti-angiogenic agents. However, kidney-related adverse reactions associated with these agents clinically manifest as hypertension and proteinuria, the most severe form being thrombotic microangiopathy (TMA). We present the spectrum of pathological features in VEGF inhibitor-associated kidney disease. Clinicopathological findings of kidney disease were retrospectively studied in 5 cancer patients treated with anti-VEGF agents. Although 4 cases received bevacizumab (anti–VEGF-A), one was given sorafenib (small molecule tyrosine kinase inhibitor affecting VEGF-R2). All patients presented with acute kidney injury, hypertension, and/or proteinuria. All kidney biopsies showed recent and chronic endothelial injury of varying severity and vascular sclerosis, including 2 with typical active features of TMA. Furthermore, acute tubular injury with focal necrosis was seen in all cases. While administration of VEGF inhibitor was discontinued in 4 cases, it was resumed for 5 more doses, following steroid therapy in 1 case. Cessation of VEGF inhibitor therapy was successful in reversing anemia and led to improvement of hypertension and proteinuria in 4 of the 5 cases. One case with TMA progressed to end-stage renal disease. A range of renal pathologic lesions secondary to endothelial injury are noted often accompanied by acute tubular damage following anti-VEGF therapy, the most severe being TMA. While most of the clinical manifestations are reversible with discontinuation of therapy, the role of other nephrotoxic chemotherapeutic agents in enhancing renal injury including severe TMA and other host factors with possible poor outcome should be considered.

1. Introduction

Vascular endothelial growth factor (VEGF) signal transduction is crucial as a regulatory system of vascular

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development during embryogenesis (vasculogenesis) and neo-vasculature formation for tissue repair in adult (angiogenesis) [1]. VEGF is also a central mediator of tumor-related angiogenesis, with increased expression, which determines prognosis in some of the solid tumors [2]. In the last decade, VEGF inhibitors have been developed as anti-angiogenic strategies to aid in cancer therapy [3]. As specific agents, VEGF inhibitors include a number of neutralizing anti-VEGF antibodies and those that target the VEGF receptors (VEGFRs), the most common being bevacizumab (Avastin), which was approved by the United States Food and Drug Administration (FDA) in 2004 [1]. When given in combination with chemotherapy or as single-agent administration, bevacizumab has been shown to prolong the survival of patients with colorectal, lung, and breast cancer. Small-molecular-weight VEGFR tyrosine kinase inhibitors used for cancer therapy include sunitinib (Sutent, SU11248), sorafenib (Nexavar, BAY 43–9006), axitinib (Inlyta, AG013736), and pazopanib (Votrient, GW786034), which inhibit multiple receptors, such as VEGFR-1, 2, and 3; platelet-derived growth factor receptor β; FMS-like tyrosine kinase 3 (Flt-3), and c-Kit protein [1].

These selective targeting agents are generally tolerated well with less frequency of life-threatening toxic effects and untargeted organ damage. However, a number of clinical trials and basic experiments with VEGF inhibitors have demonstrated frequent occurrence of dose-related nephrotoxicities, such as hypertension and proteinuria [4,5], where severe hypertension has occasionally lead to discontinuation of the VEGF inhibitor. However, the incidence and severity of proteinuria is less common than that of hypertension, and appeared to be less critical clinically secondary to glomerular abnormalities during treatment with VEGF inhibitors. Though rare, a more serious VEGF inhibitor–associated kidney injury, thrombotic microangiopathy (TMA), is a well-documented complication [6,7]. Characteristically, the manifestation of TMA in the patients with bevacizumab administration appears to be localized in the kidney, with little or no involvement of systemic microvasculature [6]. Several biopsy-proven cases have been reported with bevacizumab and other forms of VEGF inhibitors, which revealed glomerular and/or arterial TMA [6,8–14]. Experimental data have shown that VEGF inhibitors are implicated in glomerular injury [7]. Overall, human clinical trials, biopsy-proven exceptional cases, and animal experiments indicate that VEGF inhibitors are likely to result in glomerular disease during long-term treatment.

Herein, we analyzed the clinicopathologic findings of kidney injury in 5 patients with administration of VEGF inhibitor for cancer therapy, the spectrum of parenchymal features and pathophysiologic mechanisms in cancer patients. A review of the frequency of kidney-related adverse effects in previously reported clinical trials using VEGF inhibitors, documented anecdotal and series of renal biopsy cases, and the role of concomitant nephrotoxic agents are discussed.

2. Materials and methods

2.1. Case series, pathological features, and immunohistochemistry

Five cases treated with VEGF inhibitors and with kidney disease are identified from our renal biopsy files from 2008 to 2010. The kidney biopsies were processed in the renal pathology laboratory at Weill Cornell Medical College, Cornell University, New York, using standard techniques for light microscopy, immunofluorescence, and electron microscopy. Demographic, clinical, laboratory, and follow-up data with pathological findings were obtained from retrospective chart review, summarized in Tables 1–3. Immunohistochemical stain on paraffin-embedded tissue was performed using rabbit polyclonal antibody to hemoglobin (Dako North America Inc, Carpinteria, CA) on 3 cases suspected of having hemoglobin-containing tubular casts, using Bard Max Autostainer (Leica Microsystems, Buffalo Grove, IL).

2.2. Research ethics

This study was approved by the institutional review board of Weill Cornell Medical College, Cornell University, Ithaca, NY, as well as Memorial Sloan-Kettering Cancer Center, New York, NY. Informed consent of patients was not required by the institutional review board because the study was a retrospective review of clinical records and pathological results only.

3. Results

3.1. Clinical and laboratory findings

The clinical, laboratory and treatment information of the 5 patients are shown in Table 1. The age range was 55 to 67 years, and 4 of 5 were women, treated for glioblastoma multiforme, breast, colon and lung cancer, and metastatic tumor of unknown origin. Clinical renal manifestations developed 2 to 15 months after therapy with bevacizumab in 4 cases and sorafenib in 1 case. All patients presented with acute kidney injury. One patient had worsening of pre-existing hypertension (case 5), and 3 with new onset hypertension, all requiring anti-hypertensive medication. Proteinuria and hematuria were observed in 3 cases, none of which were nephrotic and ranged from 0.9 to 2.6 g/24 hours. Case 3 revealed transient hemoglobinuria due to intravascular hemolysis. Renal biopsy was performed in 2 cases because of acute kidney injury (AKI) without urinary findings (cases 2, 5). Regarding hematologic abnormalities, 3 patients were clinically diagnosed with TMA (cases 1–3) according to typical symptoms including AKI, hemolytic anemia, and thrombocytopenia, and 1 patient was suspicious for TMA (case 4). Lastly,