Clinics in Oncology

Case Report
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Bevacizumab Monotherapy for Metastatic Renal Cell Carcinoma in a Pediatric Patient

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Abstract

Renal cell carcinoma rarely occurs in children and adolescents. Localized disease has good prognosis, whereas distant metastasis have poor prognosis, with no effective therapy. Recently, 10% to 20% of adult patients have shown an apparent response to immunotherapy; however the limited pediatric experience confirms a very poor prognosis. We present a case from a patient with renal cell carcinoma with liver metastasis who has been treating with bevacizumab for ten years. She is doing well, without side effects, presenting reduction in size and number of the liver nodules.

Introduction

Renal Cell Carcinoma (RCC) is a rare entity in pediatric age, representing only 0.3% of all neoplasms of this period [1] and, from all the malignant renal tumors in children, corresponds to 3.5%. However, in children aged 15 to 19 years, accounts for 70% of the renal cancers [2]. As a rare entity in children, robust studies as in adult literature are impossible to be found. The milestone therapy for RCC in children and adolescents remains radical nephrectomy. While targeted therapy has become the first line therapy for adult metastatic RCC, there are currently literatures showing their role in children, despite that, its use must be considered for pediatric patients with unresectable, metastatic or advanced-stage RCC [3]. We present a case from a patient with renal cell carcinoma with liver metastasis who has been treating with bevacizumab with a good disease control and response.

Case Presentation

In October 2011, an 8-year-old Caucasian female was referred to Hospital Pequeno Principe, in Curitiba-PR, Brazil. She complained of swelling on the left side of the abdomen for the last month. The swelling had gradually progressed and the patient presented with hematuria. She had no family history of neoplasms and her past pathological history showed no remarkable events.

The physical examination showed an abdominal mass, slightly firm, non-mobile in the left upper quadrant of the abdomen that did not cross the midline. Other aspects of the physical examination were within normal limits. She did not present with syndromic characteristics.

The abdominal Magnetic Resonance (MRI) showed a mass in the left kidney, while the right was normal; it also showed multiple cysts and nodules in the liver parenchyma. There wasn't calcification, lymph node enlargement and vascular invasion (Figure 1).

At that time, she was submitted to a total left nephrectomy and to a liver nodular biopsy. The pathology showed a clear cell carcinoma including the liver nodule (Figure 1). She had no pulmonary metastasis and both PET-CT scan and cranial MRI were normal. The lab tests were also normal.

Since November 2011, the patient has been treating on bevacizumab 5 mg/kg each 15 days, with no side effects. In addition to clinical examination and lab tests every 15 days, she has been following with abdominal MRI each 6 months. The liver nodules have been reducing in size and number (Figure 2). In March 2017 she had another liver biopsy which was still positive.

At the end of this report, the girl is 18 years old and remains asymptomatic. She is attending school, maintaining good academic records and practicing sports without limitations. She did not have any problems in her pubertal development, including weight and height.

Discussion

Renal cell carcinoma can happen as a sporadic case or be associated with familial syndromes,

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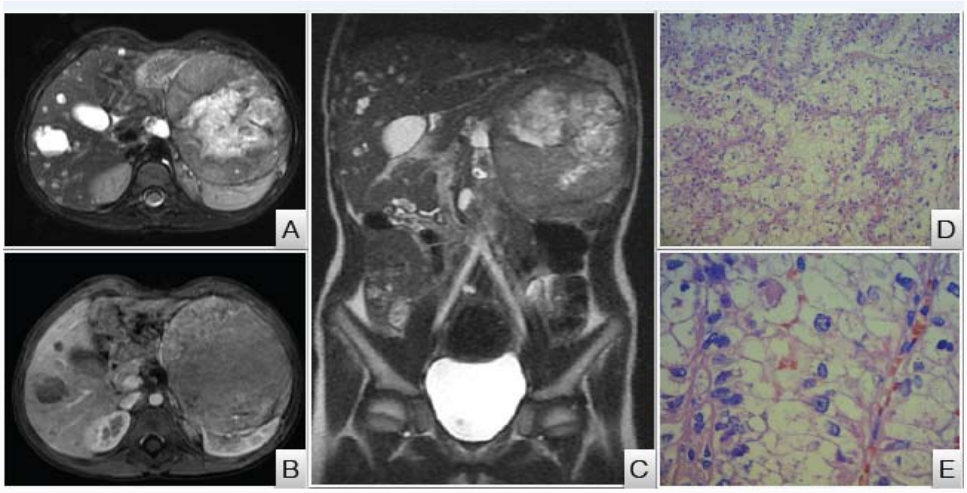

Figure 1: MRI (diagnosis - October 2011). A) T2, B) T1 with contrast, C) T2 coronal, D, E) Pathology confirmation.

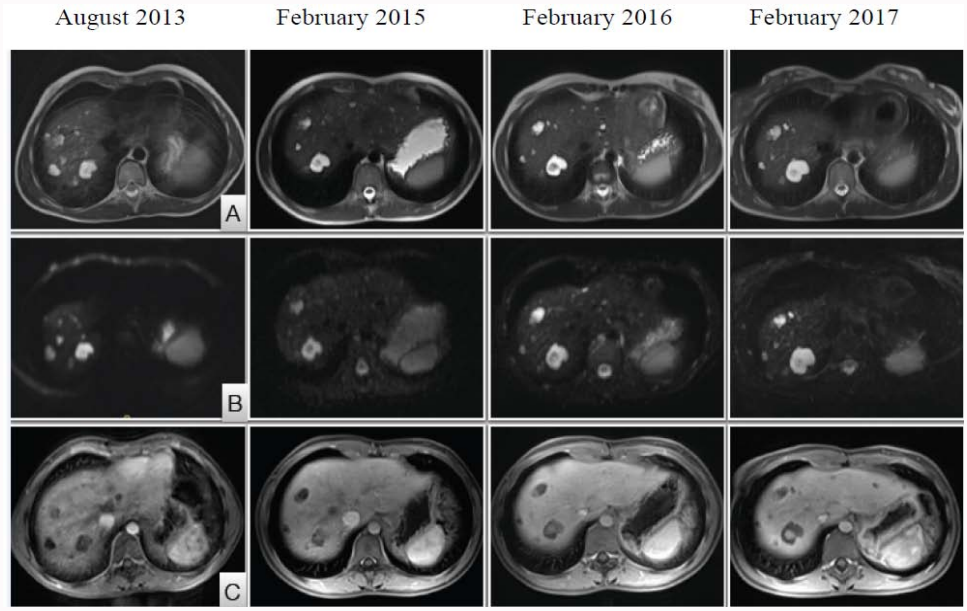

Figure 2: MRI: A) T2, B) DWI (Diffusion Weighted Imaging), C) VIBE (3D-Volumetric Interpolated Breath-hold Examination) sequence dynamic contrast-enhanced scan.

which is more frequent in younger ages and associated with Von Hippel-Lindau syndrome [4]. This syndrome consists in alterations in the tumor suppressor gene VHL, on chromosome 3p25-26 that increases the risk of clear renal cell carcinoma in children [5].

The Von Hippel-Lindau tumor suppressor gene (VHL) is mutated in the hereditary and in most cases of sporadic RCC [6]. As a consequence of these mutations, we have the overproduction of Vascular Endothelial Growth Factor (VEGF), by a mechanism that involves hypoxia-inducible factor, therefore, the Von Hippel-Lindau protein participates in the angiogenesis process [7]. VEGF is a cornerstone in angiogenesis, especially in processes of embryogenesis, ovulation, healing, and tumor growth [8]. All of those biological characteristics directed the scientific interest in the treatment of RCC with antiangiogenesis therapy drugs that are studied in clinical trials [9].

In 1997, Presta et al. [10] used the murine anti-human VEGF Monoclonal Antibody (muMAb VEGF) A.4.6.1, previously studied in mice's and showed to suppress angiogenesis in human tumor cells transplanted to those models and humanized it. The recombinant humanized MAb VEGF, bevacizumab, was thought to be a suitable strategy in the treatment of solid tumors in humans.

In the phase 1 testing, bevacizumab showed a low toxicity, had approximately 21 days of half-life, and did not induce antibodies to itself. Severe toxic effects were: Infrequent intratumoral bleeding (including fatal hemoptysis), pulmonary emboli, and peripheral venous thrombosis [11].

Since its known that RCC is characterized by aberrant angiogenic signaling and an immunogenic tumor microenvironment, systemic targeted therapies have advanced in the studies about advanced or metastatic disease. Bevacizumab has previously shown antitumor activity in RCC as monotherapy or associated with interferon α and is under investigation in clinical trials in combinations involving other

immune checkpoint inhibitors [12].

A study comparing two doses of bevacizumab and placebo in metastatic RCC, enrolling 116 adult patients, with median follow up of 27 months presented only 4 patients with partial response with a response rate for high-dose bevacizumab of 10% (95% confidence interval, 2.9% to 24.2%) [13].

Two randomized phase III clinical trials compared the combination of bevacizumab plus interferon with interferon alone, in patients who had not received a previous treatment and suffered from metastatic RCC [14,15]. The trials showed statistical best results for the bevacizumab arm, in terms of prolonging survival (Rini: 8.5 *vs.* 5.2 months; Escudier: 10.2 *vs.* 5.4 months). The prolongation of survival was related to the availability and practice of subsequent treatment after the study treatment was completed [11].

The Italian Pediatric Hematology and Oncology Association (AIEOP) studied 14 metastatic RCC patients, from January 1973 to November 2010, with a median age at diagnosis of 155.5 month. The patients were divided in groups who received chemotherapy, immunotherapy or adjuvant antiangiogenic therapy. The 2 patients who received adjuvant antiangiogenic therapy relapsed to the lungs and died 18 and 32 months after diagnosis [13].

In IMmotion151, a 2019 phase 3 trials enrolled 915 patients with metastatic RCC, comparing atezolizumab associated with bevacizumab *vs.* sunitinib as first-line therapy. The median progression-free survival was 11.2 months in the atezolizumab plus bevacizumab group *vs.* 7.7 months in the sunitinib group. In this study, 40% of the patients in the atezolizumab plus bevacizumab presented grade 3 to 4 adverse effects [16]. In this case, bevacizumab has been an effective treatment, for 9 years and 4 month, free of adverse events, promoting event-free and progression-free survival and may be allowing a future surgery approach, in order to remove the remaining liver nodules.

Conclusion

Renal cell carcinoma is a very rare entity in Pediatric Oncology, counting for 3.5% of all malignant renal tumors in children. Its main treatment consists in total nephrectomy. Targeted therapy remains well established for adult patients, but still not well studied in pediatric population. We presented a case of a female 14 years old teenager with renal cell carcinoma and liver metastasis, who has been treating with bevacizumab (pos left nephrectomy), since her 8 years old, presenting a very good image response and control and persisting asymptomatic.

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