Clinical Oncology: Case Reports

Case Report

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Challenging Radical Nephrectomy after Treatment with Nivolumab

Fernanda Nascimento Lubianca[1], Nicole Bernd Becker[1], Aline Petracco Petzold[1], Carolina Knorst Kepler[1], Carolina de Mello Viera[1], Laura Gazal Passos[1], Rafael Nazário Bringhenti[2], André P Fay[3] and Gustavo Franco Carvalhal[4*]

Abstract

Advanced Renal Cell Carcinoma (RCC) is a lethal urologic neoplasm. In cases of local progression and symptoms or in the case of a complete or significant response in the metastatic sites after systemic therapies, Cytoreductive Nephrectomy (CN) is selectively considered. Recently, it has been suggested that the use of Immune Checkpoint Inhibitors (ICIs) prior to CN could be associated with increased fibrosis and adhesions in and around the affected kidney, although the literature is scarce and controversial in this regard. Some authors postulate that the induction of the inflammatory reaction caused by ICIs on the tumours may result in significant perioperative morbidity. Aiming to contribute to the elucidation of this matter, we report a case in which nivolumab was used prior to a difficult CN in a patient with metastatic RCC, leading to an increased difficulty in performing the surgery.

Keywords

RCC; Nivolumab; Immune checkpoint inhibitors; Renal surgery; Surgical complications

Introduction

Advanced Renal Cell Carcinoma (RCC) is a lethal urologic neoplasm, with up to 15%-20% of cases being metastatic at presentation (*de novo* mRCCs) [1]. Cytoreductive Nephrectomy (CN) has been re-evaluated in this scenario, due to recent prospective, randomized clinical trials showing that systemic treatment may result in similar clinical outcome [2, 3]. However, CN is still widely considered, especially in cases of local progression and symptoms or in the case of a complete or significant response in the metastatic sites after systemic therapies [4]. Since 2015, with the approval of nivolumab, Immune Checkpoint Inhibitors (ICIs) have been effective in the treatment of metastatic RCCs, being currently used both as second and, in combination, as first line therapies [5]. Recently, it has been suggested that neoadjuvant ICIs may complicate CN due to increased fibrosis and adhesions in and around the affected kidney, although the literature is scarce and controversial in this regard [6]. We report a case in which nivolumab has been used prior to a difficult CN in a patient with mRCC.

***Corresponding author:** Gustavo Franco Carvalhal, Department of Urology, Pontifical Catholic University of Rio Grande do Sul, Rua Santo Inácio, 500 apt. 501, Moinhos de Vento, Porto Alegre, RS, Brasil, E-mail: gcarvalhal@terra.com.br

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Case Presentation

A 57 years-old female presented at the emergency room in January 2015 with a recent onset of left lumbar pain and fatigue. An abdominal Computerized Tomography (CT) showed an 8.7 cm solid lesion in the left kidney, and an enlarged periaortic retroperitoneal lymph node (4.0 cm × 3.5 cm). A chest CT revealed left subpleural nodules, suggestive of metastases. A CT-guided biopsy of the retroperitoneal lymph node disclosed a poorly differentiated carcinoma with clear cell features, suggestive of metastatic clear cell RCC. At that time, the oncology team from a different institution started the patient on weekly vinblastine, with good clinical response; chemotherapy was maintained for 11 months but had to be stopped due to hematologic toxicity (pancytopenia), and progressive cough and dyspnea. At this point, she came for a second opinion. Patient was restaged, and the chest CT showed a moderate left pleural effusion and subpleural lesions, and mediastinal lymph nodes (Figure 1). The patient was then submitted to a left pleurodesis, and biopsy of the pleura and the mediastinal lymph nodes confirmed metastatic clear cell RCC. Pazopanib was then initiated (800 mg/day PO) in March 2016. Two months later, restaging revealed the appearance of enlarged retroperitoneal lymph nodes, of a left inguinal lymphadenopathy, and of a 4.8 cm × 3.4 cm left subpleural lesion defining progressive disease by RECIST. In September 2016 the patient started on nivolumab 3 mg/Kg every 2 weeks in the expanded access program. There was no toxicity related to the ICI, and there was both a clinical and a radiological response in the chest CT (Figure 2) in the first restaging. The left inguinal lymph node also reduced in size. In August 2017, in spite of the stability of the thoracic lesions, and of a slight reduction in size of the primary tumor (Figure 3), the patient presented with worsening of the left lumbar pain, and an open CN was recommended, and performed through an anterior abdominal incision. The impression of the surgical team was that there was an intense inflammatory reaction and scar tissue surrounding the left kidney and in the retroperitoneum. The nephrectomy was very difficult due to the absence of normal surgical planes. Pathologic report showed an 8.2 cm × 8.0 cm × 5.6 cm clear cell RCC with lymphovascular invasion (pT3a, pN0). Surgical margins were negative. Non neoplastic renal cortical parenchyma revealed tubular and interstitial diffuse fibrosis and intense lymphomononuclear infiltrate (Figure 4). The patient recovered uneventfully from the CN and was discharged home using oral everolimus. In November 2017, three months after the CN, the patient was readmitted with worsening of the general health, intense bilateral lumbar pain and reduced strength in the lower limbs. An abdominal angio-CT revealed an acute occlusion of the abdominal aorta above the iliac vessels (Leriche's syndrome); the patient was submitted to a bilateral arterial embolectomy and a femur-femoral bypass but complicated with hemodynamic instability and cardiorespiratory arrest.

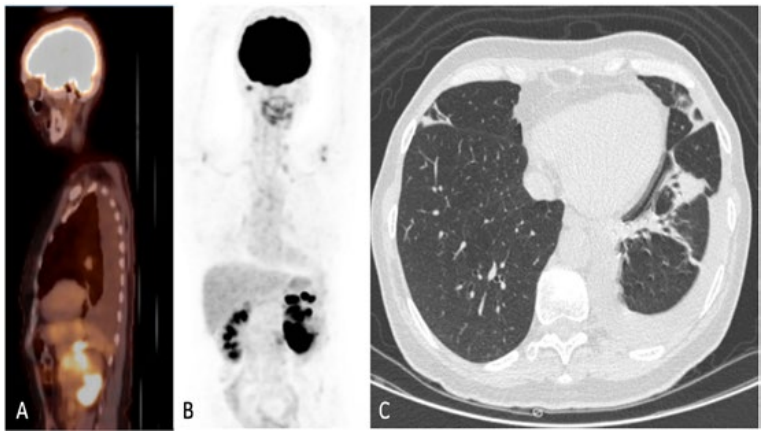

Figure 1: Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) (A, B) and Chest CT (C) showing a moderate left pleural effusion, subpleural lesions, and mediastinal lymph nodes.

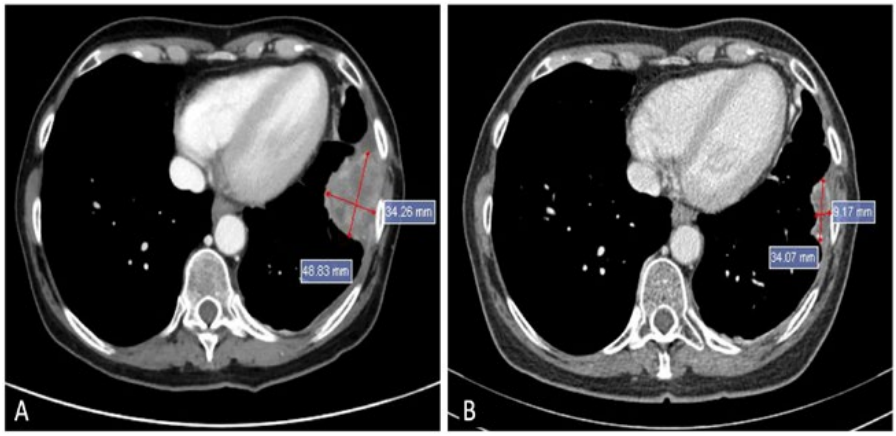

Figure 2: Chest CT showing radiological response to nivolumab in a subpleural lesion (A, B).

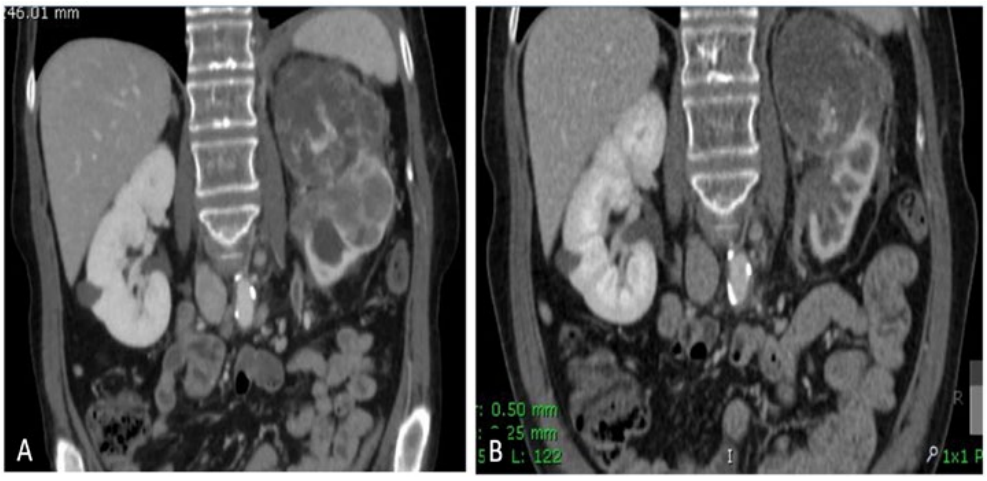

Figure 3: Abdominal CT showing a slight reduction of the size of the primary tumour (A, B).

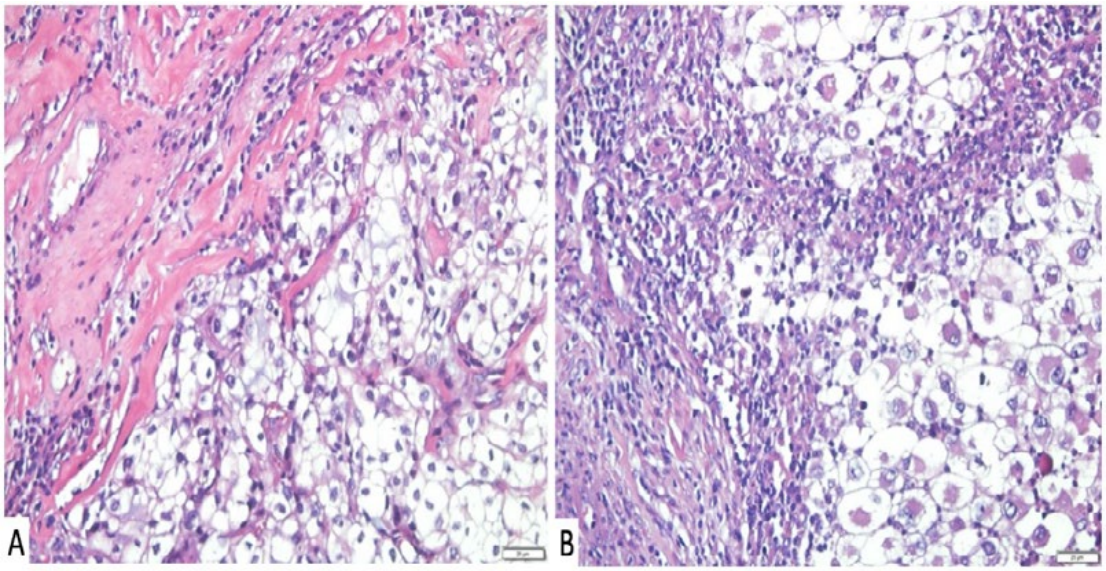

Figure 4: Haematoxylin and Eosin (H and E) stained slides (×200), revealing peritumoral fibrosis and mild peritumoral chronic lymphomononuclear inflammation (A), and rhabdoid differentiation, peritumoral fibrosis and more significant chronic peritumoral lymphomononuclear inflammation (B).

Discussion

Until recently, Tyrosine Kinase Inhibitors (TKIs) were the preferred first line treatment to metastatic RCCs. In the neoadjuvant setting, these drugs were often associated with altered coagulation and healing. Most authors recommended the suspension of these therapies at least two weeks prior to surgery in order to avoid surgical morbidity. The introduction of ICIs as a therapeutic option in metastatic and advanced RCC has revolutionized the care of this disease. In 2015, nivolumab was approved as a second-line therapy; subsequently, ICIs were approved as first line therapies in 2017 due to more durable responses and prolonged overall survival in phase II studies and phase III clinical trials. [7] However, not much is reported in the medical literature regarding the effects of ICIs on subsequent surgery when patients need surgical intervention after using this class of medication.

Some authors postulate that the induction of the inflammatory reaction caused by ICIs on the tumors may give rise to technical difficulties during subsequent surgery, such as difficulty in finding normal dissection planes which may result in significant perioperative morbidity. Pignot et al., reported that in 11 patients treated with nivolumab, alone or in association with ipilimumab or tivozanib, surgery was more challenging than usual, leading to a change in the surgical approach during the procedure in two cases. In their series, postoperative complication rate was 54.6%, including two major complications and one surgery-related death [6].

On the other hand, various case series and cohort studies of neoadjuvant ICIs and subsequent nephrectomies do not mention technical difficulties or an increase in perioperative complication rates or deaths. Singla et al published a study with ten patients whose nephrectomy was performed after neoadjuvant treatment with nivolumab or with the combination of nivolumab plus ipilimumab, reporting no conversion to open surgery in patients operated through a minimally invasive approach [8]. Therefore, controversy remains on the issue of surgical safety after neoadjuvant use of ICIs.

Conclusion

We report a case of a multi-treated patient with mRCC who sequentially received chemotherapy (vinblastine), a tyrosine kinase inhibitor (pazopanib) and a novel ICI (nivolumab) prior to a CN indicated because of worsening of local symptoms. Surgery was deemed as extremely challenging by the surgical team due to the intense scar tissue and fibrosis surrounding the kidney. We hope that this report may raise concern on the issue of CN following neoadjuvant ICIs, and we believe that these surgeries should be performed by experienced and aware surgeons.

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Author Affiliations

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[1]*School of Medicine, Pontifical Catholic University of Rio Grande do Sul, Brasil*

[2]*Department of Pathology, Pontifical Catholic University of Rio Grande do Sul, Brasil*

[3]*Head, Department of Oncology, Pontifical Catholic University of Rio Grande do Sul, Brasil*

[4]*Department of Urology, Pontifical Catholic University of Rio Grande do Sul, Brasil*