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Case Report

Downstaging and Pathological Complete Response of Locally Recurrent Sarcomatoid Renal Cell Carcinoma under Pembrolizumab and Lenvatinib: A Case Report and Review of Literature

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Renal cell carcinoma · Recurrence · Immunotherapy · Neoadjuvant therapy

Abstract
The advent of immune checkpoint inhibition opened new perspectives for patients with recurrent or metastasized renal cell carcinoma. In case of recurrent disease, surgical resection remains the most promising therapeutic option. Surgical resection is associated with improved overall survival and demonstrated curative potential given complete resection of metastases can be performed. This report presents the case of a patient with local recurrence of dedifferentiated sarcomatoid renal cell carcinoma approximately 1 year after initial open lumbar nephrectomy. After initial evaluation, surgical removal was deemed infeasible and an induction therapy with pembrolizumab and lenvatinib was initiated. After 3 months, corresponding to 5 cycles of pembrolizumab, the tumor showed a partial response on imaging control and was successfully resected en bloc. Histopathological examination of the specimen revealed no evidence of viable neoplastic cells. This is the first report describing a complete pathological response of a locally recurrent dedifferentiated sarcomatoid renal cell carcinoma after treatment with pembrolizumab and lenvatinib. Overall, the combination therapy was well tolerated with a maximum Common Terminology Criteria for Adverse Events Level of Two. These findings underline the potential of

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multimodal therapeutic strategies for recurrent renal cell carcinoma, such as induction therapies to downstage initially nonresectable masses, and highlight the need for prospective studies to allow for evidence-based treatment plans.

Introduction

Renal cell carcinoma (RCC) accounts for 2% of cancer-related deaths globally and has shown an increasing incidence rate [1]. In industrialized countries, renal masses are most frequently incidental findings on ultrasound exams or other imaging studies, such as computed tomography (CT) or magnetic resonance imaging. When malignancy of a renal mass cannot be ruled out, surgical treatment by partial or complete nephrectomy constitutes the standard of care in most cases. Only "small renal masses," defined by a diameter <4 cm and an annual growth rate of <0.5 cm, can be initially followed up with active surveillance performing repeat imaging studies. However, in case of progression, active treatment is still recommended [2]. Surgical removal of localized RCC is considered curative but, across all risk groups, a 20% recurrence rate has been recorded [3]. Available data on isolated local retroperitoneal recurrence of RCC without distant metastasis following nephrectomy is rare. Psutka et al. [4] found a 1.3% rate of isolated local recurrence in a cohort of 2,502 patients who had undergone radical nephrectomy between 1970 and 2006. In this dataset, local recurrence was associated with a worse prognosis. In accordance with established guidelines, recent data have reinforced the potential benefit of active local treatment of recurrent RCC. While some selection bias may have skewed results, patients who underwent local treatment of recurrence had an overall survival of 70.3 months (95% confidence interval 58–82.6 months), compared to 27.4 months (95% confidence interval 23.6–31.15 months) in patients not receiving local treatment of recurrence [5]. If metastasis resection or radiotherapeutic ablative techniques are not feasible, systemic therapy is a well-established approach for treating metastatic RCC (mRCC); however, it is not considered curative. Selection of first-line therapy for mRCC is based on a risk stratification approach using the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. Generally, this systemic therapy comprises either the combination of the immune checkpoint inhibitors (CPIs) nivolumab (a monoclonal antibody acting as a PD-1 inhibitor) and ipilimumab (a monoclonal anti-CTLA-4 antibody) or the combination of the CPI pembrolizumab (also monoclonal PD-1 inhibitor) and tyrosine-kinase inhibitors (TKIs), such as axitinib or lenvatinib. These combination treatments have demonstrated their potential to generate complete responses in patients with mRCC, thus drastically improving their overall prognosis. More specifically, the CPI/CPI combination achieved complete response rates of 10.1%, while the CPI/TKI combination of pembrolizumab with lenvatinib achieved 16.1% [6, 7]. In addition, these therapies exhibited distinctly higher overall survival rates compared to sunitinib treatment, further solidifying their position as today's standard of care [8, 9]. Treatment response is generally assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. In the context of treatment response, a complete response is defined as the disappearance of all target lesions and pathological lymph nodes. Conversely, a partial response is characterized by a reduction of at least 30% in the sum of the longest diameters of target lesions. If neither sufficient shrinkage for a partial response nor significant growth for progressive disease is observed, the status is classified as stable disease. On the other hand, progressive disease is defined as an increase of at least 20% and at least 5 mm in the sum of the longest diameters of target

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lesions or the appearance of new lesions. However, systemic therapies are still palliative by definition and accompanied by a substantial incidence of side effects. According to the Common Terminology Criteria for Adverse Events (CTCAE), more than 80% of patients receiving pembrolizumab and lenvatinib, and 60% of patients receiving ipilimumab and pembrolizumab develop grade III/IV side effects [9]. In this context, it is noteworthy that quality of life data remains underpublished in phase II/III trials and that the impact of prolonged antineoplastic medication on patients' life beyond survival remains poorly understood [10]. Thus, while these therapies demonstrate promising response and survival rates, it is crucial to maintain definitive therapy as the treatment goal in order to maximize the potential for persistent cure and minimize therapy-associated toxicity. In this case report, we present a compelling demonstration of the potency of these emerging agents in significantly reducing metastasis volume. Our findings highlight the potential of these novel therapies, enabling the curative resection of a previously deemed nonresectable local recurrence.

Case Presentation

In July 2021, a 49-year-old nonsmoking Caucasian female initially sought medical attention at the emergency unit of our hospital, which serves as tertiary urological referral center. She presented with an exacerbation of left flank pain persisting for several months, along with symptoms of lower abdominal pain, urge, fatigue, and myalgia. Her medical and family history indicated no significant abnormalities or family history of cancer and her ECOG performance status was 0. A CT scan revealed a 4.2 cm heterogeneous mass in the left kidney, raising suspicion of RCC. Subsequent staging, including an abdominal and thoracic CT scan, showed no evidence of metastatic disease. In August 2021, a radical lumbar nephrectomy was performed, and histopathological examination confirmed the presence of an unclassified RCC with sarcomatoid patterns. The final TNM classification of the diagnosed RCC was pT1b L0 V0 Pn0 R0 cM0 G4, indicating a poorly differentiated tumor between 4 cm and 7 cm in diameter without invasion into lymphatic vessels or adjunct nerves. Surgical margins were clear. The initial operation proceeded without any complications, and the patient was discharged for follow-up in accordance with the European Association of Urology (EAU)-Guidelines. In October 2022, the patient was again referred to our hospital due to the development of a painful, palpable mass in the left flank over several weeks. Apart from these new findings, there were no additional complicating factors, and the patient's ECOG performance status remained 0. A CT scan revealed an extensive retroperitoneal locoregional recurrence measuring 10 cm in diameter, along with a small subcutaneous metastasis measuring 1.5 cm near the previous surgical access route on the left dorsolateral flank. The recurrence and tumor mass were considered functionally nonresectable. At this time, no distant metastases were detectable. Laboratory studies were unremarkable, placing the patient in the intermediate risk group according to IMDC criteria. Considering the patient's desire to pursue active therapy, we initiated a combination therapy regimen consisting of pembrolizumab (200 mg i.v. q3w) and lenvatinib (20 mg p.o. q1d). After 3 months, the feasibility of metastasis resection was planned to be reevaluated. Overall, the combination therapy was well tolerated by the patient. Following the initial administration of pembrolizumab, the patient developed hypertension, which was managed with candesartan (8 mg q2d) and amlodipine (5 mg q1d). Additionally, the patient developed hypothyroidism, requiring L-thyroxine substitution (75 µg q1d). These adverse effects did not exceed CTCAE level II. Between October 2022 and January 2023, the patient received five doses of pembrolizumab, while lenvatinib was taken continuously as planned. Treatment adherence was maintained without any interruptions. During the planned restaging in January 2023, the masses showed a partial response

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sufficient to allow surgical treatment. In early February 2023, the surgical metastectomy was successfully performed. The resection resulted in a substantial tissue defect, requiring the application of a vacuum dressing after appropriate skin excision. Final closure of the wound was achieved through a secondary intervention involving the placement of a subfascial mash 14 days after the initial operation. Representative CT-scans are shown in Figure 1.

Pathological evaluation of the resected mass revealed a complete pathological response (ypT0) of the tumor. No unexpected wound healing defects were observed during the patient's uneventful recovery. The patient was discharged on the 16th day post-surgery, fully ambulatory. Postoperative staging CT showed no evidence of disease, indicating that the patient is now considered to be without evidence of disease. While pembrolizumab monotherapy following resection of high-risk localized RCC has been shown to increase disease-free survival but not overall survival for these patients, the standard of care following a multimodal approach, as described herein, remains undefined.

Given the current metastases-free state and sparse available data on the efficacy of adjuvant therapy after recurrence treatment, we opted to proceed with structured imaging-based follow-up according to the EAU-Guidelines on Renal Cancer. Figure 2 provides a timeline outlining the diagnostic and therapeutic events. First discussions with the patient about the potential preparation of a case report were held before the metastasectomy. A joint decision was made to draft a case report about her case regardless of the eventual pathological result of the local recurrence resection. The patient expressed that sharing their experience was important to her, because, regardless of the eventual result of the operation, other patients in similar situations could benefit from her experiences. In preparation for this case report, the authors have completed the CARE Checklist, which is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534000).

Discussion

The combination of pembrolizumab and lenvatinib is approved as a first-line treatment of mRCC across all IMDC risk groups. This regimen has demonstrated remarkable efficacy, with complete clinical response rates reaching 16%, and partial response rates at 55%. Consequently, it constitutes a standard of care drug regimen for metastasized renal cancer [7]. The efficacy of this therapeutic approach in generating a complete pathological response with only a partial clinical response according to RECIST criteria after 3 months of treatment underscores the potential of multimodal therapeutic approaches that extend beyond cytoreductive surgery or systemic therapy alone in the era of CPI and TKI. Both the EAU and the American Urological Association's guidelines on RCC acknowledge the role of active treatment for local recurrences in oligometastatic patients, highlighting that these patients may benefit from metastasectomy if the recurrence can be safely resected with clear surgical margins. According to a recent study investigating the management of locally recurrent RCC, patients who underwent surgery for locally recurrent disease in combination with systemic therapy demonstrated significant cancer-specific survival benefits. Specifically, the study reported a 3-year cancer-specific survival rate of 92% for patients treated with both local-recurrence surgery and systemic therapy. This was significantly higher than the 3-year cancer-specific survival rate of 62% observed in patients who underwent local-recurrence surgery alone [11]. The cohort analyzed in the study consisted of patients who underwent primary nephrectomy between 1988 and 2018, a period during which surgical techniques, oncological standards, and treatment options for RCC changed notably. Nonetheless, the addition of systemic therapy appears to confer a substantial and lasting survival benefit beyond that of surgical removal of oligometastases or local recurrences alone. Despite recent advances in the management of RCC, the overall prognosis for patients with RCC recurrence has

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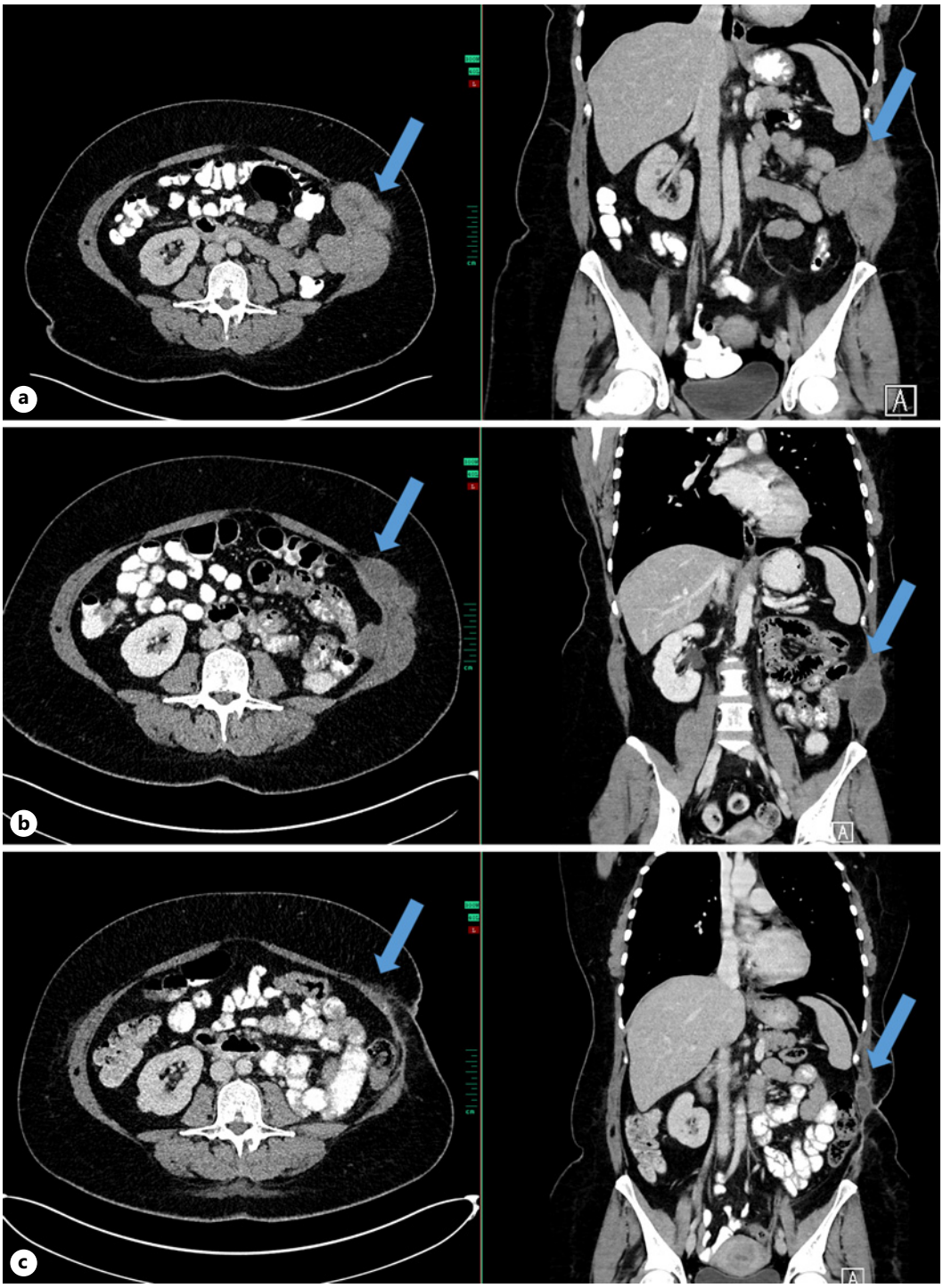

Fig. 1. Transversal and coronal planes of CT scans upon initial diagnosis of local recurrence (**a** – top), preoperatively after 3 months of treatment described as partial remission (**b** – middle), and showing a post-operative seroma (**c** – bottom).

historically remained limited and recurrence is relatively frequent. A retrospective study by Dabestani et al. [12] analyzed a cohort of 1,265 patients who received treatment for RCC with curative intent between 2006 and 2011 and reported a recurrence rate of 23%. Forty-six percent

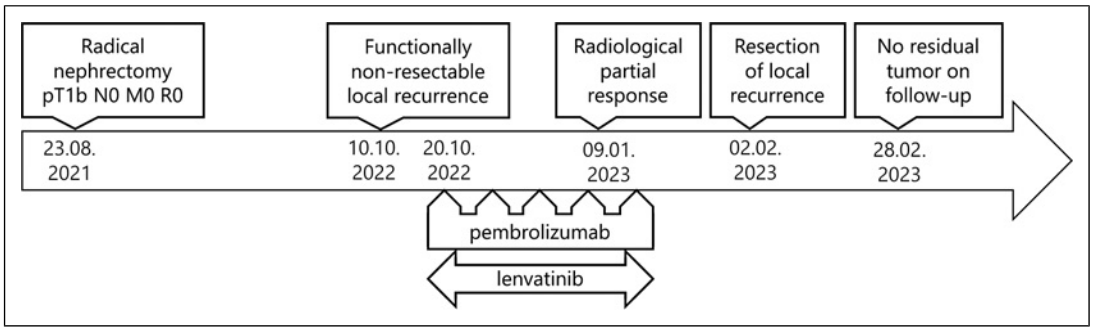

Fig. 2. Timeline of diagnostic and therapeutic events.

of patients with recurrent disease were identified as potentially curable based on the location and size of metastases. However, among these patients with potentially curable disease, only 38% survived (with or without evidence of disease) after a follow-up period of 4 years. It is important to note that these results were obtained prior to the advent of CPI and the complete pathological and clinical responses of mRCC under combination treatments of CPI/TKI or CPI/CPI, which today are seen in circa 10% of mRCC cases. Specifically, the combination of two CPI, ipilimumab and nivolumab, which is approved for IMDC high-risk mRCC, has been shown to reliably generate pathological complete responses, further underlining the potential of this drug class [13].

The case reported here represents a shift toward induction therapy, using CPI/TKI therapy to downstage a locally recurrent tumor, which enabled the successful treatment of the local recurrence through surgical resection. Furthermore, it also demonstrated the efficacy of the pembrolizumab/lenvatinib combination specifically in dedifferentiated sarcomatoid RCC, as evidenced by a complete pathological response after 3 months of treatment. Other authors have recently reported a case of mRCC achieving a complete pathological response after 1 year of pembrolizumab and axitinib [14]. In our case, we show the possibility of achieving a similar response in a significantly shorter timeframe, underlining the potential of neoadjuvant therapy for mRCC. Accordingly, the emerging knowledge of a possible pathological complete response at stable disease or partial clinical response levels presents an increasing challenge when determining the timing and patient selection for cytoreductive surgery.

Likewise, the advancement in systemic therapies such as CPI/TKI or CPI/CPI combinations may lead to new indications for subsequent surgeries. These could include increasing drug-toxicity leading to patients expressing a wish to discontinue therapy at partial response or stable disease levels of mRCC or completion of planned induction therapy to downstage an otherwise unresectable metastasis. Conversely, biopsy-confirmed complete pathological response of recurrences following systemic therapy could render some therapies of local recurrences unnecessary. We suggest further systematic studies to investigate and determine the optimal duration and CPI/TKI or CPI/CPI combination(s) for neoadjuvant and possibly adjuvant therapy and establish follow-up strategies for this group of patients.

Conclusion

With the advent of effective combination CPI/TKI therapies, multimodal treatment strategies are becoming increasingly attractive. However, to date, no biomarkers to predict the response to immunotherapy in mRCC patients have been established [15]. Thus, these therapies must be considered individual treatments and discussed as such with the patient. Nevertheless, our findings carry wider implications for clinical practice in treating

oligometastasized or locally recurrent RCC with CPI/TKI combinations. First, following therapy, residual mass resection could be performed safely, and no wound healing deficiencies were observed. By using vacuum sealing to precondition the wound prior to closure, secondary wound closure could effectively be performed, even in the presence of large operating defects. Furthermore, incomplete clinical remissions may not necessarily indicate suboptimal treatment efficacy. Therefore, obtaining biopsies of treatment-persistent masses that pose challenges for surgical or alternative management can aid in the decision-making process regarding the suitability of ablative therapy. This approach becomes particularly relevant when considering deferring active therapy in the absence of malignancy. Since the follow-up of patients with ypT0 status after resection is currently not standardized, further research in this field is necessary to define guidelines for optimal management to standardize and improve care of this likely growing group of patients.

Statement of Ethics

This retrospective review of single patient data did not require ethical approval in accordance with local guidelines. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Data collection and assembly: J. Ell, P. Balz, and P. Manava. Data analysis and interpretation: J. Ell, P. Balz, and C. Hüttenbrink. Manuscript writing: J. Ell and P. Balz. Final manuscript approval and accountable for all aspects of the work: all authors.

Data Availability Statement

The underlying data of this case study cannot be made publicly available due to the ethical risk of compromising patient privacy but is available in anonymized form from the corresponding author, J.E., upon reasonable request.

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