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Immunotherapy-induced adverse events in metastatic renal cell carcinoma: A case of rapid response and complex challenges

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ABSTRACT

A 55-year-old woman with dyspnea was diagnosed with a 9.5cm left renal clear cell carcinoma and extensive metastatic disease. Initial treatment with Sunitinib was effective but discontinued due to severe dermatitis. Nivolumab therapy led to complete metastasis resolution and consequently nephrectomy was performed at 12 months. Postoperatively, she developed Vogt-Koyanagi-Harada-like disease, necessitating Nivolumab suspension and vision improvement with corticosteroids. After 24 disease-free months, a new contralateral renal lesion and pulmonary metastases were identified, prompting cabozantinib treatment. This resulted in clinical improvement and a partial response at the first follow-up.

1. Introduction

Renal cell carcinoma (RCC), especially in its metastatic form, represents a significant health challenge, accentuated by its propensity for late-stage diagnosis, making systemic therapeutic interventions, particularly immunotherapy, pivotal. Despite its potential for altering the disease course, immunotherapy incorporates a spectrum of possible adverse events. While immunotherapeutic approaches have fundamentally altered RCC management, and thus can be perceived as a beacon of hope for addressing this significant health problem, it is imperative to understand the potential adverse manifestations to secure optimized, patient-centric outcomes in the context of metastatic RCC treatment.

2. Case presentation

A female patient in her 50s was admitted to the emergency department with an irritating dry cough that had been persisting for about a week, associated with dyspnea. She had been in contact with a patient diagnosed with tuberculosis, which led to an urgent medical evaluation. She was hospitalized in the pneumology department to receive oxygen therapy.

Her initial laboratory workup did not reveal any significant alterations, and her sputum tests for mycobacteria were negative. However, a chest X-ray showed a diffuse nodular pattern bilaterally (Fig. 1), and a subsequent chest CT scan revealed the presence of multiple centimetric nodules throughout the pulmonary parenchyma, suggestive of secondary metastatic locations. Notably, an abnormality was detected in the left kidney, characterized by a lobulated hypodense formation both pre- and post-contrast, measuring 9.5 x 7.3 × 7.2 cm, suggesting an expansive process requiring histological characterization (Fig. 2). There were also enlarged lymph nodes at the left renal hilum and a dilatation in the right kidney's collecting system. A urinary cytology was requested, which showed rare inflammatory cells and transitional cells with reactive nuclear atypia, but no neoplastic cells were detected.

Following the evaluation, and with the suspicion of an intermediate risk renal cell carcinoma (according to the International Metastatic RCC Database Consortium), the urology team decided to proceed with a cytoreductive nephrectomy. However, during the preoperative assessment, it was determined that the patient was not fit for anesthesia due to the progressive worsening of the dyspnea. A new CT scan confirmed rapid progression of the disease, and with the clinical degradation the patient was experiencing, a decision was made to not resuscitate (DNR) in case of cardiac or respiratory arrest. A plan was devised to perform percutaneous biopsies of the mass, optimize her respiratory function with the help of the pulmonology department, verify the histology, and initiate systemic therapy.

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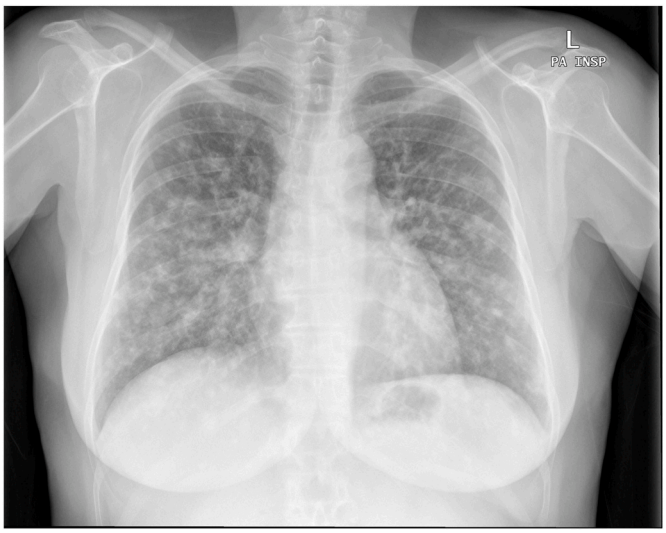

Fig. 1. Initial chest X-ray showing an extensive diffuse nodular pattern bilaterally.

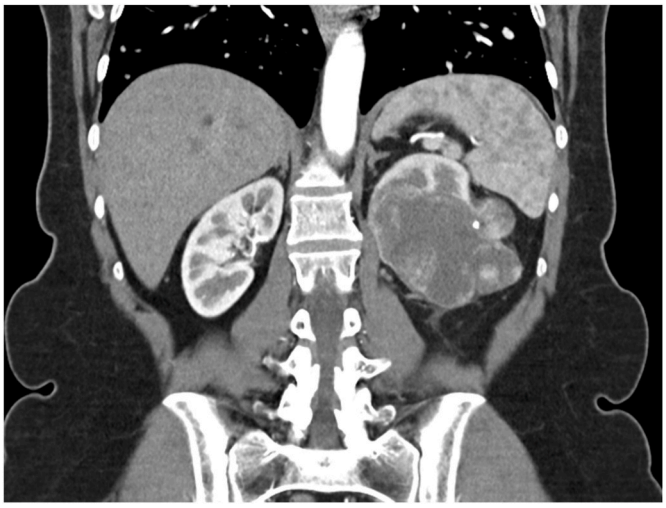

Fig. 2. Abdominal CT scan displaying an aggressive 9.5cm left renal mass.

Renal mass histology revealed a clear cell RCC with sarcomatoid differentiation, International Society of Urologic Pathologists (ISUP) grading 4. Sunitinib, a tyrosine kinase inhibitor, was prescribed to manage her metastatic renal cell carcinoma, as the sole therapeutic option reimbursed by the national health system at the time. Sunitinib was prescribed, in a dose of 50mg a day with 2 weeks interval without sunitinib each 4 weeks, and soon showed clinical improvement, with resolution of the dyspnea and partial response on control CT scan.

3. Outcome and follow-up

After 5 months of treatment with sunitinib, the patient began to develop debilitating skin adverse reactions. The most severe of these was a dermatitis of the hands that proved unresponsive to corticoid therapy (Fig. 3). Attempts to manage the side effects by reducing the dosage of sunitinib or switching to a 2 week on/1 week off schema were unsuccessful. Consequently, sunitinib had to be withdrawn due to the severity of the skin toxicity. On the 10th month after diagnosis, the patient started therapy with nivolumab, a PD-1 inhibitor, with a dose of 240mg every 2 weeks after careful consideration of the patient's previous adverse reactions.

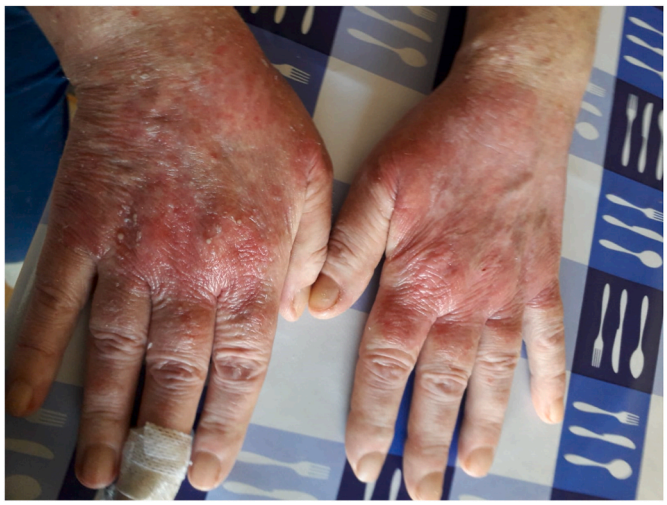

Fig. 3. Severe dermatitis of the skin (hands), secondary to Sunitinib.

The patient's first imaging control, conducted 3 months after the initiation of nivolumab treatment, revealed a complete response in terms of the secondary lesions, with only the primary renal lesion remaining in the left kidney, now measuring 7.5 cm. These promising results were discussed in a multidisciplinary meeting, and it was decided to proceed with a cytoreductive nephrectomy 14 months after the initial diagnosis. The histology of the resected kidney confirmed the previous results and estimated a tumor regression of 50 %.

Two months post-surgery, control imaging showed no evidence of disease, marking a significant milestone in the patient's treatment history. However, at this stage, the patient began experiencing a sudden loss of visual acuity. She was thoroughly evaluated by the neurology department; a cranial CT scan and lumbar puncture revealed no abnormalities. The ophthalmology department's examination determined that the patient's visual acuity had decreased to less than 1/10 bilaterally, with an observed thickening of the choroid throughout the eyeball. Given these findings, a diagnosis of a Vogt-Koyanagi-Harada-like syndrome, a panuveitis characterized by rapid vision loss, was made, assumed to be secondary to the immune checkpoint inhibitor nivolumab.

Nivolumab was promptly discontinued 16 months after diagnosis and the patient was then treated with intravitreal corticosteroid injections, which resulted in a modest improvement of visual acuity. Regrettably, bilateral cataracts developed subsequently and the patient underwent successful cataract surgery in both eyes, which improved her visual acuity to 8/10 bilaterally, significantly improving her quality of life.

A multidisciplinary meeting concluded that nivolumab would be discontinued due to the severe adverse reaction and the patient's achieved complete response. The treatment plan was adjusted to active surveillance.

For 15 months after stopping nivolumab, the patient showed no signs of disease. At the 32-month mark from the initial diagnosis, a control CT scan detected a 0.9 mm lesion in the right kidney. A biopsy followed by an ablation of the renal mass was carried out three months later. The biopsy confirmed renal cell carcinoma with sarcomatoid differentiation, and the ablation procedure was completed without incidents.

Three months following the ablative therapy, the patient presented to the emergency department with a dry cough and dyspnea. Chest X-ray indicated a significant pleural effusion, which was drained, providing symptom relief.

A control CT scan showed an 8.2 cm right renal lesion, a large right-sided pleural effusion, multiple secondary lesions in the pleura and pulmonary parenchyma, as well as mediastinal and lumbo-aortic lymphadenopathies.

In the subsequent 30 days, the patient repeatedly visited the emergency department, requiring hospitalization for respiratory function management and multiple thoracenteses.

The case was revisited in a multidisciplinary meeting, and treatment with cabozantinib was approved, commencing at 40 months post-diagnosis.

Post initiation of cabozantinib, the patient reported significant improvement in dyspnea and did not seek healthcare services for dyspnea or new pleural effusion formation again.

Currently, 3 months after starting cabozantinib, imaging control has shown a partial response, with a reduction in the size of the renal mass and all pulmonary and nodal lesions.

4. Discussion

This case presents a complex interaction between therapeutic efficacy and adverse effects in the context of metastatic renal cell carcinoma (RCC). The initial response to nivolumab and subsequent severe ocular side effects poses a challenging balance of risk versus benefit. A literature review reveals a paucity of cases detailing Vogt-Koyanagi-Harada (VKH)-like syndrome associated with nivolumab, highlighting the uniqueness of this case.[1] Mechanisms of immune checkpoint inhibitor (ICI)-induced panuveitis, similar to VKH, are thought to involve a T-cell mediated attack on melanocytes, which are present in the uveal tract of the eye,[2] with most cases reported representing adverse ocular events to immunotherapy in the context of metastatic melanoma.

Emerging retrospective studies indicate a possible link between immune-related adverse events and the efficacy of therapy.[3] In this case, the patient showed a definitive response to both sunitinib and nivolumab, albeit accompanied by significant adverse effects.

Current clinical guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) emphasize the importance of tailored treatment strategies in advanced RCC. These strategies consider factors such as patient performance status, the profile of adverse events, and specific histological characteristics of the tumor. Consistent with these guidelines, the management of ICI-related adverse events in this case involved discontinuing the causative agent and starting corticosteroid therapy.[4]

The case highlights the importance of monitoring for ocular side effects in patients treated with ICIs and demonstrates the potential for effective responses with second line therapeutic agents. This report contributes to the evolving understanding of the management of complex RCC cases, especially those exhibiting unusual responses or experiencing rare adverse effects from systemic therapy.

CRediT authorship contribution statement

João Pedroso Lima: Investigation, Writing – original draft. **Ana Marta Ferreira:** Validation. **Vasco Quaresma:** Validation. **Manuel Lopes:** Validation. **João Lorigo:** Investigation. **Paulo Azinhais:** Writing – review & editing. **Pedro Nunes:** Writing – original draft. **Arnaldo Figueiredo:** Writing – review & editing.

Declaration of competing interest

There are no conflict of interests to report.

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