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A case of metastatic renal cell carcinoma with concomitant Castleman's disease treated with immunotherapy

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ABSTRACT

Brief abstract: Castleman's disease (CD) is an uncommon lymphoproliferative process that can present concurrent to other solid organ malignancy, especially in selected populations. Concomitant CD and renal cell carcinoma (RCC) are challenging in terms of diagnosis and treatment. Assessment of CD involvement is a crucial step in selecting the optimal treatment strategy. Here we report a case of metastatic RCC and concurrent CD treated with surgery and immunotherapy.

Introduction

In recent years, many effective systemic treatments have been introduced for the treatment of advanced renal cell carcinoma (RCC) such as Vascular Endothelial Growth Factor Receptor tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin inhibitors and immune checkpoint inhibitors (ICIs).[1] Today, ICIs are considered the most effective systemic treatment for metastatic RCC (mRCC).

Concurrent presentation of lymphoproliferative diseases can complicate the staging and optimal treatment planning in mRCC. Furthermore, the impact of lymphoproliferative diseases on response to ICI is not known. Castleman's disease is a lymphoproliferative disorder that is neither purely reactive nor purely neoplastic in nature. Depending on the extent of lymphoid tissue involvement, CD may present either as unicentric (UCD) or multicentric (MCD) lymphoid hyperplasia. Determining the extent of lymphoid tissue involvement is a crucial step in the management since the two types differ in etiology, treatment, and prognosis.[2]

The diagnostic challenge and potential impact of elevated IL-6 and anemia in concurrent RCC and CD presentation have been previously reported.[3] To the best of our knowledge, this is the first report on the use of ICIs in the management of a patient with a concurrent diagnosis of mRCC and UCD.

Case presentation

A 57-year-old male presented with bilateral lower extremity swelling after a 10+ hour plane flight. He reported night sweats and fevers up to 39.4 °C. Initial workup was negative for deep vein thrombosis, but hematuria, proteinuria, significant anemia with hemoglobin of 10.7 g/dL (range 13.6–17.2) and elevated inflammatory markers with LDH of 230 U/L (range 125–220) and C reactive protein of 11.0 mg/dL (range 0.0–1.0) were noted.

Computed tomography (CT) of the abdomen and pelvis showed a large right renal mass (Fig. 1) with tumor thrombus extending into the inferior vena cava (IVC, Fig. 1A, arrow), multiple small pulmonary nodules, retroperitoneal lymphadenopathy and an atypical left lower quadrant mass (Fig. 1B, arrow) suspicious for lymphoproliferative disease, given the history of night sweats and fever. The patient underwent an extensive rheumatologic and infectious workup, which was negative. MRI of the head did not show any central nervous system metastases. CT guided renal mass biopsy showed clear cell RCC, histologic grade 4, with

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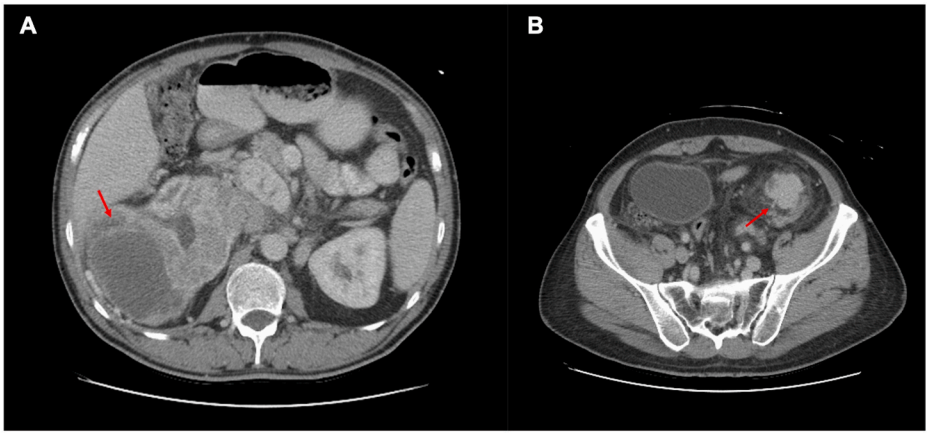

Fig. 1. Computed tomography of the abdomen at diagnosis. A. Large renal mass and tumor thrombus extending into the inferior vena cava (arrow). B. An atypical left lower quadrant mass suspicious for lymphoproliferative disease.

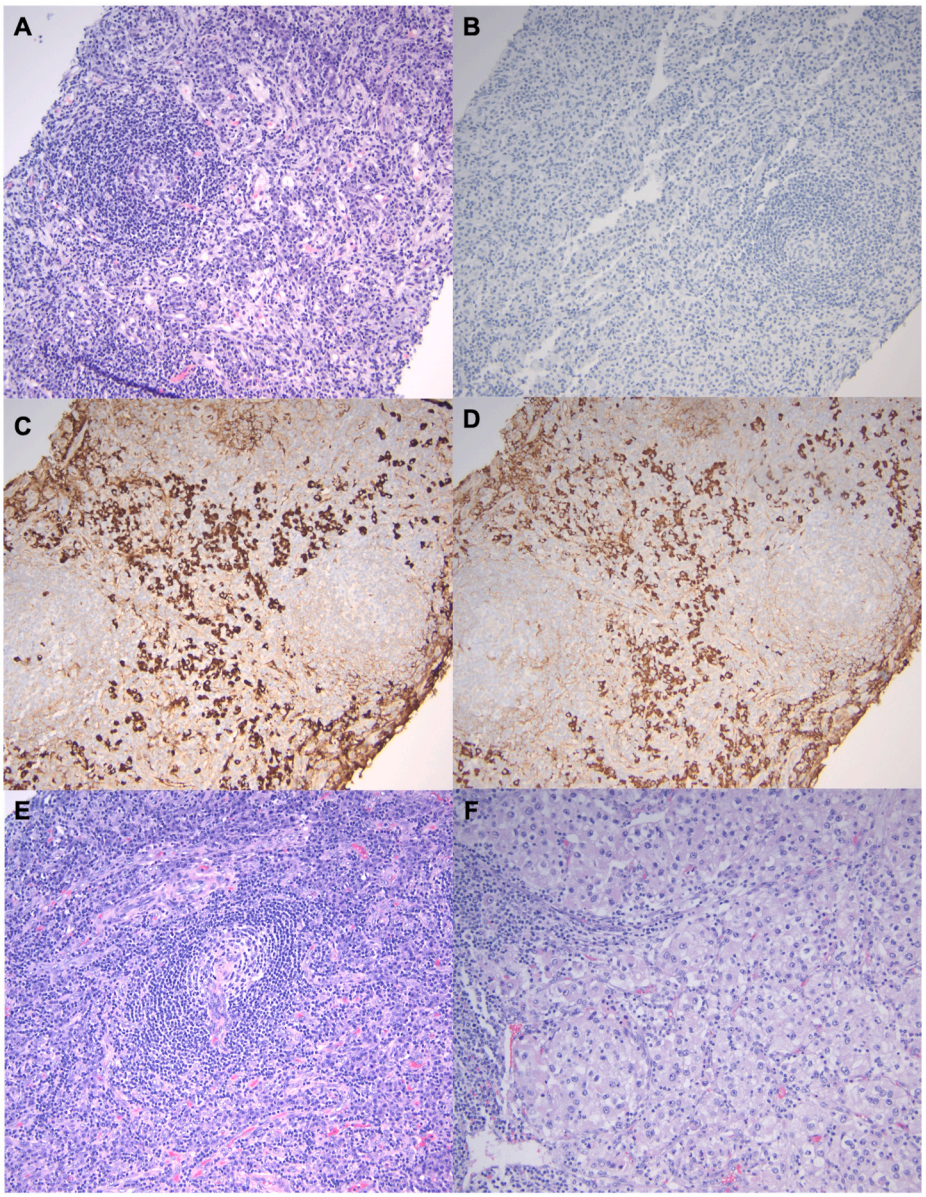

Fig. 2. A–D: Immunohistochemistry (IHC) evaluation of the biopsy specimens from the left lower quadrant abdominal mass. (20× magnification). A. Hematoxylin and eosin staining show a lymphoid follicle with an atretic germinal center and a central vessel, with the background showing vascular proliferation and increased plasma cells. B. HHV 8 staining was negative. Kappa (C) and Lambda (D) staining showed increased plasma cells that are present in an interfollicular distribution and are polyclonal by kappa and lambda IHC. E–F: Surgically resected lymph nodes (20× magnification). E. Perinephric lymph node involved by renal cell carcinoma. F. Left lower quadrant abdominal mass. Atretic germinal center traversed by a prominent central hyalinized vessel ("lollipop follicle"), onion-skin appearance of the surrounding mantle zone, and interfollicular vascular proliferation. These are characteristic pathologic findings for CD, which were present in this specimen.

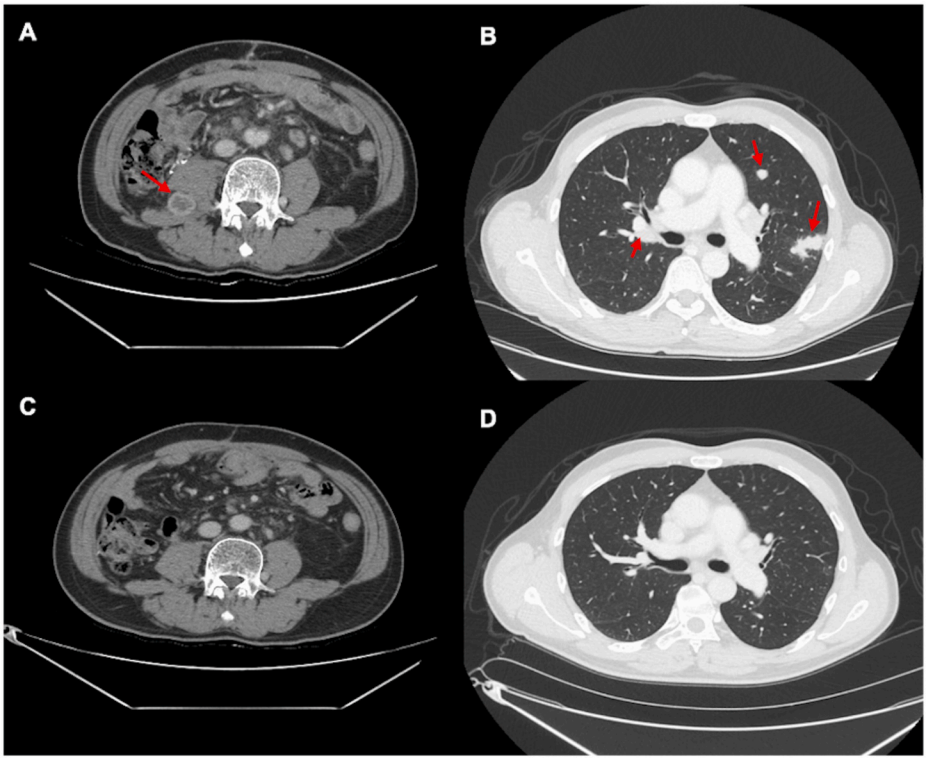

Fig. 3. Computed tomography images of the thorax and abdomen. A. Increase in retroperitoneal lymph nodes before starting treatment with ipilimumab/nivolumab (Ipi/Nivo) B. Pulmonary metastases before starting Ipi/Nivo. C. A marked decrease in the size of retroperitoneal lymph nodes after 4 cycles of Ipi/Nivo. D. Near-complete resolution of pulmonary metastasis after 4 cycles of Ipi/Nivo.

rhabdoid features. A biopsy of the left lower quadrant abdominal mass was also attempted but showed only benign-appearing lymphoid tissue.

Considering the large primary renal mass (comprising more than 75% of the patient's total disease burden), the large IVC thrombus, and overall good performance status, cytoreductive nephrectomy (CN) was recommended. A repeat biopsy of the left lower quadrant abdominal mass demonstrated "benign reactive lymphoid tissue with increased polyclonal plasma cells and some Castleman-like features" (Fig. 2, A-D). This specimen was negative for carcinoma, and there was no evidence of IgG4 disease or Rosai-Dorfman disease. HHV8 staining was negative (Fig. 2B). The patient underwent CN, IVC thrombectomy, retroperitoneal lymph node (LN) dissection, and left lower quadrant abdominal mass excision. Pathology confirmed RCC of right kidney, nuclear grade 4, with rhabdoid features. All of the eight resected retroperitoneal LNs were involved with RCC (Fig. 2E). The resected left lower quadrant abdominal mass was found to be a LN with changes consistent with UCD (Fig. 2F). Repeat CT scans showed an increase in the size of retroperitoneal and mediastinal LNs, new and enlarging pulmonary metastases, and multiple new peritoneal metastases (Fig. 3, A& B). The patient subsequently started systemic treatment with ipilimumab and nivolumab (Ipi/Nivo).

His scans after 4 cycles of Ipi/Nivo showed a partial response to treatment with a marked decrease in the size of enlarged LNs and near-complete resolution of multiple peritoneal and pulmonary metastasis (Fig. 3C and D). He continued Nivolumab maintenance therapy per approved standard of care treatment protocol. His anemia completely resolved after the first two cycles of Ipi/Nivo. Except for mild itching and dry skin, the patient has been tolerating treatment very well. CT scans at six months after starting treatment showed a continued response.

Discussion

This is the first report of immunotherapy in the treatment of concomitant mRCC and CD. The concurrent diagnosis of RCC and CD introduced challenges in selecting the optimal treatment approach. The first question was the sequence of CN and systemic treatment. Historically, CN was shown to improve survival in patients with mRCC who were treated with interferon-alfa. However, in the era of more effective systemic treatments, the benefit of CN is questioned. Current evidence supports the clinical relevance of CN in selected mRCC patients undergoing targeted or immunotherapy treatments.[4] Our patient presented with multiple retroperitoneal LNs. An accurate assessment was crucial to distinguish between RCC and CD and determine the extent of CD (UCD vs. MCD). In contrast to the indolent nature of UCD, MCD usually requires systemic treatment with monoclonal antibodies targeting CD20 (Rituximab) or IL-6, glucocorticoids, or chemotherapy[2] and this would have further complicated treatment selection. Pathological evaluation of CN surgical specimens showed that of all resected retroperitoneal LNs were involved by RCC. The left lower quadrant abdominal mass was the only lesion with CD pathologic characteristics, making UCD the most likely diagnosis. As all resected retroperitoneal LNs were involved with only RCC, complete surgical resection was considered the definitive CD treatment.

Considering the patient's overall good performance status, we wanted to select a systemic treatment regimen with the highest chance of a complete response for his mRCC. Our patient had intermediate-risk mRCC (as defined by International mRCC Database Consortium criteria) for which combination regimens (ICI/ICI or TKI/ICI) are the current standard of care.[1] However, the rate of complete response to ICI/ICI was higher than TKI/ICI and a longer duration of follow up is available for patients treated with ICI/ICI.[5] Another consideration was the impact of the treatment regimen on wound healing after CN. Selecting TKI/ICI combination would have delayed the start of systemic treatment after CN to allow adequate recovery and healing time.

In conclusion, concurrent presentation of CD can complicate the accurate staging and optimal treatment selection in patients with solid tumors. Response to immunotherapy in patients with

immunoproliferative disorders such as CD and other concurrent malignancies would be worth investigating.

Declaration of conflict of interest

None.

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Consent

The authors certify that we have obtained appropriate patient consent to use his images and other clinical information in this publication.

Author contributions

Drafting of the manuscript and case presentation - Taja Lozar, Matthew Brunner; Literature review and discussion: Taja Lozar, Matthew Brunner; Histopathology image – Sujal Shah; Revision of the manuscript: Hamid Emamekhoo, Christos Kyriakopoulos; Supervision: Hamid Emamekhoo, Christos Kyriakopoulos. All authors have read and approved the final manuscript.

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