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Immuno-oncology therapy associated thromboembolic events in metastatic renal cell carcinoma

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ABSTRACT

The relationship between thromboembolic events (TEs) and immune-oncology (IO) agents in patients with metastatic renal cell carcinoma (mRCC) with inferior-vena-cava (IVC) thrombus has not been explored despite conferring significant morbidity.

A late 30s female is diagnosed with mRCC with a level-II IVC thrombus after presenting with back pain. Two weeks post initiation of immunotherapy, she re-presented with bilateral sub-massive pulmonary emboli requiring IVC and pulmonary thrombectomy.

This case exposes a potential relationship between mRCC and IVC thrombus with IO agents that creates a critically hypercoagulable state. This issue requires further investigation given the apparent under-reporting of TEs in these patients.

1. Introduction

Immune-oncology (IO) has significantly changed the face of cancer treatment and its role in patients with metastatic renal cell carcinoma (mRCC) is well established. We report a case of a woman aged in her late 30s with mRCC and level II IVC thrombus who developed a life-threatening pulmonary embolus (PE) after commencement of treatment with a single round of IO agents. Thromboembolic events (TEs) carry considerable morbidity and mortality risks as 72% of immune-related TEs end in hospitalisation. Several studies have reported an increased rate of TEs with immunotherapy[1] with rates in mRCC quoted to be 12% at 12.8 months median follow-up.[1] Patients receiving IO agents have an increased risk of TEs over patients without IO therapy for mRCC in the range of 1.3% for local disease and 4.3% in metastatic disease.[1] No studies have explored the relationship between IO ages and RCC with inferior vena cava (IVC) thrombus and specifically how IO treatment may affect the stability of the IVC thrombus. We report a case of a female in her late 30s with mRCC and extension of tumour thrombus to the IVC who developed multiple recurrent sub-massive PEs following a single round IO therapy.

2. Case presentation

A female in her late 30s presented to a major metropolitan emergency department with severe back pain and was found to have a large renal mass with a level II IVC thrombus on imaging (Fig. 1), bone metastases to T9 and L4 invading the L4 nerve root, liver metastasis and involvement of intra-abdominal and supradiaphragmatic lymph nodes. Histologic analysis of L4 vertebral body biopsy demonstrated a fumarate hydratase deficient RCC. She was subsequently started on her first cycle of ipilimumab and nivolumab. Two weeks later she represented with bilateral sub-massive PEs (Fig. 2) and right heart failure. She underwent catheter-directed thrombolysis and subsequent thrombectomy with the left pulmonary artery cleared and two thirds of the right pulmonary artery cleared. A repeat CT pulmonary angiogram with contrast and abdomen and pelvis 3 days following this procedure was found to have the similar pulmonary clot burden despite treatment.

Due to concerns about recurrent PEs from the potentially unstable IVC thrombus, the decision was made to perform an IVC and pulmonary thrombectomy with cardio-pulmonary bypass. A cytoreductive left nephrectomy was not performed due to extensive adherence of the kidney to the surrounding major vessels and structures. Intraoperatively, a grade II IVC tumour thrombus was identified and was completely evacuated. The patient was stable in ICU postoperatively. Three weeks after her thrombectomy, she was found to have residual tumour thrombus extending the length of left renal vein to within the infra-renal IVC which is partly opacified with presumed tumour thrombus, with no extension to the supra-renal IVC (Fig. 3). At this stage she was started on

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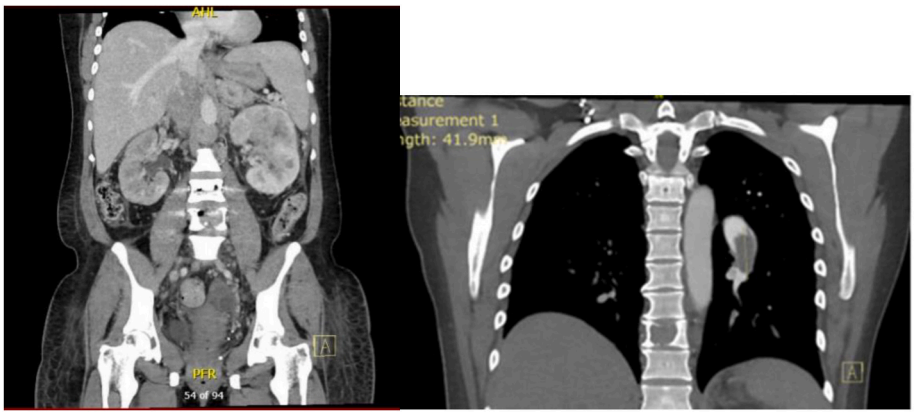

Fig. 1. Coronal CT Chest/abdomen/pelvis demonstrating RCC with extension of IVC thrombus above renal vein but below hepatic vein (Level II).

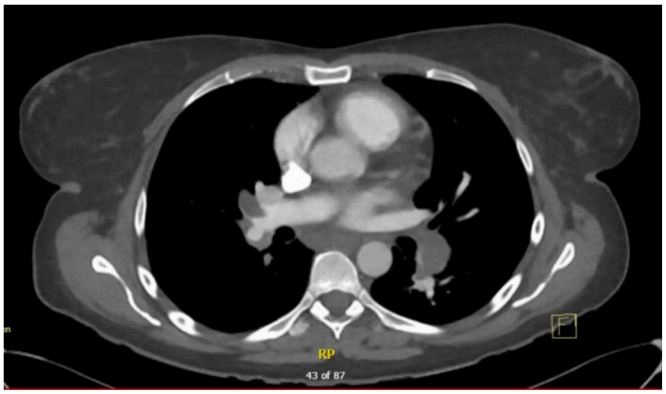

Fig. 2. CT pulmonary angiogram demonstrating bilateral sub-massive pulmonary emboli.

Cabozantinib. Interval scanning 3 months later demonstrated a reduction in the size of the primary lesion with a persistent tumour thrombus with the same partial opacification of the infra-renal IVC with nil suprarenal IVC extension.

3. Discussion

This case report seeks to explore the relationship in RCC patients with IVC thrombus who develop TEs post IO agents. The mechanism of IO agents inducing TEs is unclear, but one mechanism is thought to be due to the proinflammatory status induced by IOs which enhance a prothrombotic state by increasing coagulation and platelet activity and impairing fibrinolysis.[2] One case report of Pembrolizumab induced acute thrombosis reported that the sudden onset of T-cells immediately after initiation of treatment could be associated with thrombosis.[3]

Another mechanism of TE and sub-massive PE post IO treatment in extensive IVC thrombus would be tumour necrosis of the thrombus creating an unstable thrombus. It is well established in patients with mRCC, who have extension of tumour thrombus to the IVC, have increased risk of VTE. Therefore, it cannot be stated whether this case was due to a baseline increased risk in TEs or due to potential efficacy of IO agents causing subsequent necrosis of the IVC thrombus. This uncertainty is exacerbated by an apparent under-reporting of TE in studies investigating IO agents in advanced cancers, including renal cell carcinomas with IVC thrombus.[4]

However, an analysis of mRCC in 351 patients with intermediate to poor risk disease revealed that patients were at an increased risk of venous and arterial TEs 6 months after initiation of IO therapy and can persist for years.[1] Additionally, a case report of a 47-year-old male with

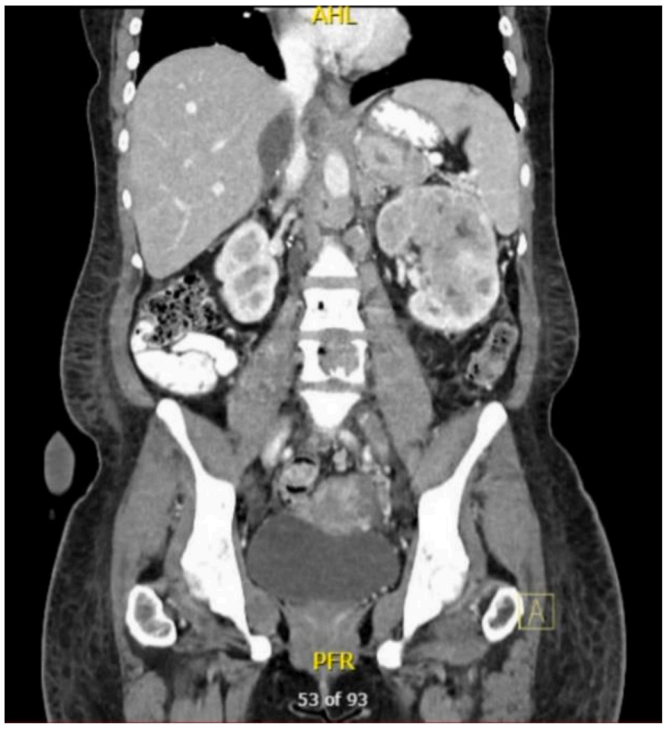

Fig. 3. CT abdomen post thrombectomy demonstrating clearance of suprarenal IVC tumour thrombus and persistent tumour thrombus extending through the left renal vein with partial opacification infrarenal IVC, presumed due to tumour thrombus.

mRCC and IVC tumour thrombus who at baseline had no evidence of PE or deep venous thrombosis and had an IVC filter insitu was started on nivolumab. One year after initiation of treatment but 4 months following investigations demonstrating absence of TEs, he developed a diffuse distribution of thromboses in superior and inferior mesenteric veins, splenic vein and portal vein5 that parallels a significant hypercoagulable state post IO therapy which occurs in our case.

Immunotherapy for advanced renal cell carcinoma is a rapidly evolving field that has yet to be fully explored. Despite its numerous apparent benefits, our case of a female in her late 30s with mRCC and IVC thrombus developed sub-massive PEs requiring IVC and pulmonary artery thrombectomy following one course of IO therapy. The immediate critically hypercoagulable state post initiation of IO agents accentuates the need for further studies in patients with mRCC with IVC thrombus to give patients the most informed decision about their

treatment.

Declarations

Ethics approval was gained through Austin Health (Victoria, Australia) Human Ethics Committee, and the patient has signed an Austin Health Human Ethics Committee consent form. Both the patient and ethics committee has given consent for publication.

There are nil competing interests or funding for this manuscript.

All authors contributed in the writeup, editing and preparation of the manuscript.

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List of Abbreviations:

mRCC: Metastatic Renal Cell Carcinoma
IVC: Inferior Vena Cava
IO agents: Immune-oncology agents
VTEs: Venous thromboembolism
TEs: Thrombembolic events
PE: Pulmonary Embolus