



Treatment of metastatic TFE3 microphthalmia transcription factor translocation renal cell carcinoma: a case report

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Background: Microphthalmia-associated transcription factor/transcription factor E (MiTF/TFE) translocation renal cell carcinoma (RCC) is a rare type of non-clear cell RCC (nccRCC), which is more common in females. Currently, there is no standardized treatment for advanced metastatic microphthalmia translocation RCC (MiT-RCC). The main treatment modalities include surgery, chemotherapy, immunotherapy, anti-vascular endothelial growth factor or vascular endothelial growth factor receptor (VEGFR) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and targeted therapy against the mesenchymal-epithelial transition (MET) factor signaling pathway.

Case Description: We present the case of an 8-year-old male patient with hematuria and paroxysmal urinary pain. Based on tumor genetic testing results and targeted drug matching analysis, the patient underwent tumor biopsy, tumor radical surgery with vascular osteotomy, and cervicothoracic lymph node dissection. The patient was then treated with a combination of immunotherapy [sintilimab, a drug directed against programmed cell death receptor-1 (PD-1)] and VEGFR tyrosine kinase inhibitor (TKI) (from pazopanib to sunitinib). Throughout the 10 cycles of conventional chemotherapy (seven courses of sintilimab since the start of the third chemotherapy treatment), the patient's condition remained stable, with no tumor recurrence at the primary site. However, in the later stages, the patient developed a large amount of ascites, and the family requested discontinuation of treatment, ultimately leading to the patient's death.

Conclusions: In this case report, we summarize the therapeutic strategy of a young patient with metastatic transcription factor E3 (TFE3) MiT-RCC. For this disease, early immunotherapy and the use of precision-targeted drugs may have a favorable impact on the survival prognosis of the patient but may still be of less benefit in children with advanced multiple metastases. Therefore, further research on tumor driver genes, among other treatment components, is urgently needed to improve precision therapy.

Keywords: Case report; MiTF/TFE translocation renal cell carcinoma (MiTF/TFE translocation RCC); treatment; TFE3

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Introduction

Transcription factor E3 (*TFE3*) microphthalmia transcription factor translocation renal cell carcinoma (MiT-RCC) is a rare and aggressive renal malignancy, which is significantly more prevalent in children (40%) than in adults (4%) (1). MiT family translocation RCCs mainly include Xp11 translocation renal cell tumors carrying *TFE3* gene fusions and t(6;11) RCCs carrying transcription factor EB (*TFEB*) gene fusions (2). The basic helix-loop-helix leucine zipper transcription factor of the microphthalmia-associated transcription factor/transcription factor E (MiTF/TFE) (MiT) family consists of four closely related members: *MiTF*, *TFE3*, *TFEB*, and *TFEC* (3). The MiTF/TFE family is now thought to play a key role in organelle biogenesis, nutrient sensing, and energy metabolism (4).

Mutations and/or aberrant expression of MiTF/TFE family members have been associated with different types of cancers in humans, such as renal carcinomas, alveolar

sarcomas, and melanomas (4). MiTF/TFE family factors are also involved in the regulation of lysosomal signaling, including mTOR complex 1 (mTORC1) and the Wnt/ β -catenin pathway, which are critical for oncogenic signaling (5,6). Most metastatic RCCs are treated with tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor receptor (VEGFR), including pazopanib, sunitinib, sorafenib, bevacizumab, ramucirumab, and cabozantinib (1,7-9). Here, we report a case of advanced metastatic *TFE3* MiT-RCC, for which we employed a combination of surgery, chemotherapy, immunotherapy, and targeted therapy. However, the patient eventually developed a significant amount of ascites (including a large number of tumor cells). The family expressed a low willingness for further treatment and decided to discontinue therapy, resulting in the patient's eventual death. We hope that this single-center case can provide new insights into the treatment of metastatic *TFE3* MiT-RCC. We present this article in accordance with the CARE reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-24-35/rc>).

Highlight box

Key findings

- This report summarizes the therapeutic strategy for a case of metastatic of transcription factor E3 (*TFE3*) microphthalmia transcription factor translocation renal cell carcinoma (MiT-RCC), which included immunotherapy (sintilimab) and administration of vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) (from pazopanib to sunitinib).

What is known and what is new?

- At present, the main treatment methods for advanced metastatic MiT-RCC include surgery, chemotherapy, immunotherapy, anti-vascular endothelial growth factor or VEGFR inhibitors, mammalian target of rapamycin inhibitors, and targeted therapy against the mesenchymal-epithelial transition factor signaling pathway.
- In this case report, although the patient's tumor mutational burden and microsatellite instability analysis results suggested limited potential benefit from immune-checkpoint inhibitor monotherapy, sintilimab was nonetheless administered based on the patient's condition. Due to suggestions gathered at the 4th Congress of Chinese Research Hospital Association-Children's Oncology Committee-Multidisciplinary Treatment, we changed the treatment of TKIs targeting VEGFR from pazopanib to sunitinib.

What is the implication, and what should change now?

- The current treatment mode for malignant tumors is molecular diagnosis and tailored treatment. For patients with advanced metastatic *TFE3* MiT-RCCs, there is an urgent need to develop immunotherapy and identify novel targeted therapeutic agents to improve the survival of these patients.

Case presentation

The patient was an 8-year-old boy who attended the local hospital with gross hematuria and intermittent urinary pain for 2 weeks, without frequency or urgency. He was initially examined at a local hospital, where a computed tomography (CT) scan (*Figure 1*) revealed a malignant tumor in the lower and middle poles of the left kidney. Our CT examination confirmed a mass measuring approximately 35.2 mm × 31.0 mm × 36.8 mm in the lower pole of the left kidney and a mass of about 40.3 mm × 28.0 mm × 65.1 mm in the anterior aspect of the left kidney, suggestive of a renal tumor with retroperitoneal lymph node metastasis. Local invasion of the renal capsule by the tumor was also observed (*Figure 1A,1B*). Positron emission tomography-CT (PET-CT) demonstrated similar findings and no new distant metastases.

After a multidisciplinary discussion at our center, considering the difficulty of complete resection due to the tumor's size and the need for a definitive diagnosis, we performed a tumor biopsy surgery. Immunohistochemistry of the postoperative tumor sample (*Figure 2A,2B*) demonstrated positivity for *TFE3*. Fluorescence in situ hybridization (FISH) testing for *TFE3* on the tumor sample revealed a breakpoint frequency of 44% (44/100, randomly counting 100 tumor cells), surpassing the threshold of 20%. Microscopically, the tumor cells were seen to have a

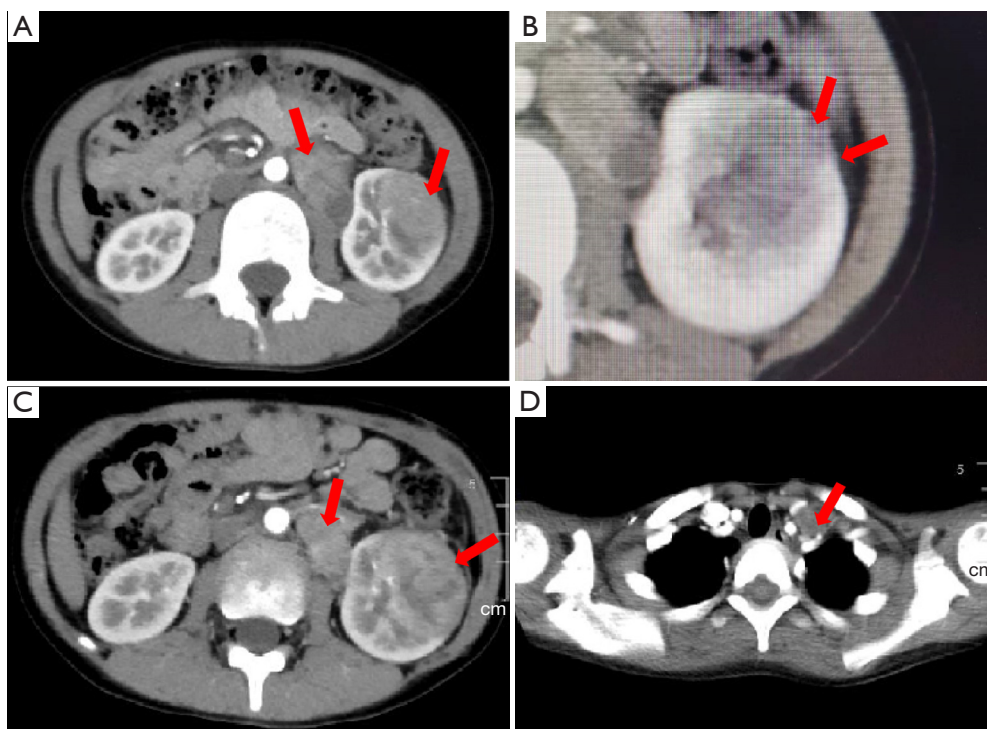


Figure 1 CT images of the patient at different stages of treatment. (A) CT images from our hospital at the time of the patient’s initial consultation. Red arrows indicate the location of the tumor and the possibility of retroperitoneal lymph node metastasis. (B) CT at initial diagnosis: after enhancement, the mass strengthened unevenly with signs of extravasation through the renal peritoneum. Red arrows suggest that the tumor is suspected to have breached the renal envelope. (C) Repeat CT images after three regular treatments. Red arrows suggest progression of the tumor as well as retroperitoneal lesions. (D) Enlarged lymph node shadow in the left supraclavicular fossa indicative of tumor metastasis. Red arrow indicates an enlarged lymph node on the inner side of the left supraclavicular fossa. CT, computed tomography.

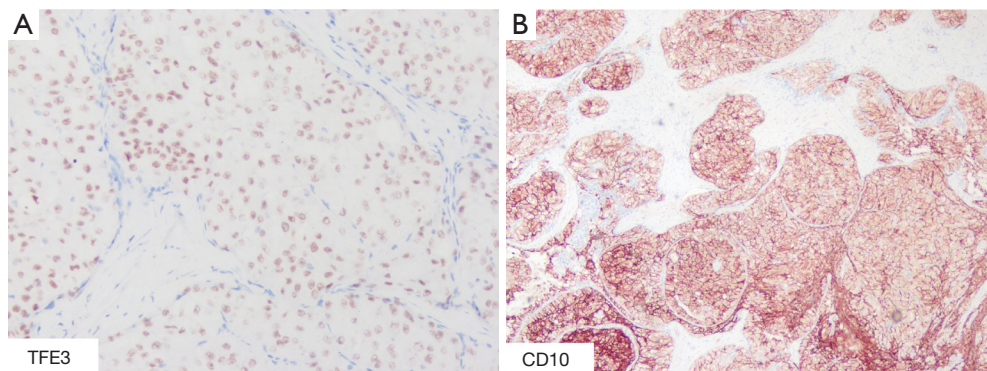


Figure 2 Immunohistochemistry of the tumor. (A) Transcription factor E3, 200×; (B) CD10, 100×.

papillary structure, and gravel bodies were scattered within the tumor tissue. Based on these findings, the patient was diagnosed with stage T4N1M1 IV *TFE3* MiT-RCC.

Following the surgery, the patient received two cycles of chemotherapy primarily consisting of cyclophosphamide

and doxorubicin. Follow-up CT scans revealed an increase in the size of the left renal mass and the retroperitoneal tumor (*Figure 1C*), and ultrasound indicated lymph node metastasis in the neck. Subsequently, we incorporated sintilimab [a fully human immunoglobulin G4 (IgG4)

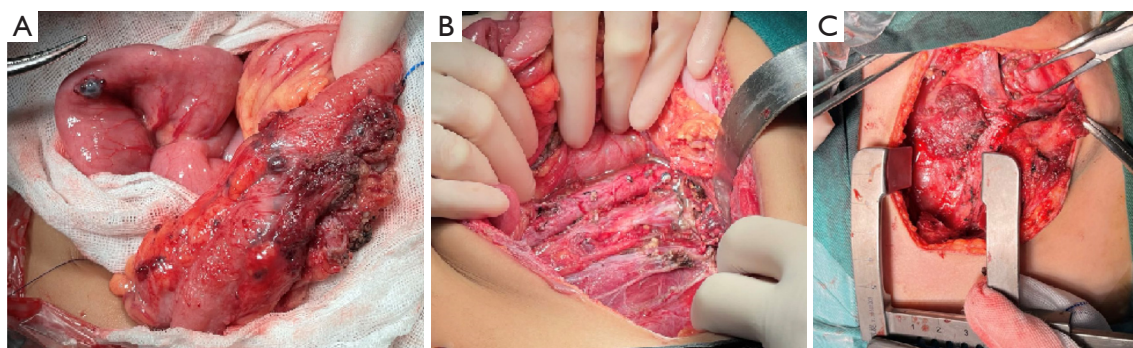


Figure 3 The intraoperative findings of nephrectomy for renal cancer (A,B) and left supra-cervical mediastinal lymph node lesion dissection (C).

monoclonal antibody that binds to programmed cell death receptor-1 (PD-1)] into the subsequent chemotherapy regimen. Since the third chemotherapy, the patient has received a total of seven courses of sintilimab.

After three cycles of chemotherapy, we performed radical nephrectomy with vascular osteotomy and clearance of multiple tumor implants in the abdominal cavity. Pathological examination confirmed metastases in the perirenal area, small intestine, colon, mesocolon, greater omentum, para-aortic lymph nodes, paracaval lymph nodes, and iliac vascular lymph nodes, consistent with the previous findings (Figure 3A,3B). The patient received sintilimab and additional chemotherapy before and after the surgery, respectively.

The test results for the 831 genes related to the tumor, in combination with the targeted drug matching analysis, indicated that the tumor was microsatellite stable (MSS) with a tumor mutational burden (TMB) of 0.00 muts/Mb. Additionally, a mutation of *PALB2*-p.Glu650Ter (heterozygous nonsense mutation, 49.3%), which is a member of the DNA damage response (DDR) pathway genes, was detected in the patient. *DDR* gene mutations lead to an increase in TMB value and infiltration of lymphocytes in the tumor, making patients with *DDR* gene mutations more likely to benefit from immunotherapy (10). Furthermore, considering the personalized analysis of chemotherapy drug sensitivity, we adjusted the chemotherapy regimen for the patient to achieve precision treatment. During the fifth round of chemotherapy, we incorporated the targeted drug, pazopanib, in addition to the sintilimab-based chemotherapy regimen.

At the 4th Congress of Chinese Research Hospital Association-Children's Oncology Committee-Multidisciplinary Treatment (CRHA-COC-MDT), which was hosted by our center on August 28, 2022, we shared and discussed this case with all major pediatric solid tumor centers

in China. It was suggested that we change the targeted drug from pazopanib to sunitinib. During the sixth round of chemotherapy, a thoracotomy was performed in collaboration with the Thoracic Surgery Department to remove the lymph node metastasis in the supraclavicular region. Surgery was also performed to clear the extensive metastatic lymph nodes in the left superior cervical mediastinum (Figure 3C). During the eighth round of chemotherapy, the treatment regimen was changed to sintilimab + sunitinib + chemotherapeutic drugs. In the tenth round of chemotherapy, the patient developed a large amount of ascites, which was not detected in the previous routine ultrasound examination. Ascitic fluid smear revealed tumor cells, and intraperitoneal chemotherapy was administered. However, the patient responded poorly to the treatment. In the eleventh round of chemotherapy, abdominal ultrasound indicated liver metastasis of the tumor. Due to the family's low willingness to continue, they ultimately decided to forgo further treatment, after which the patient died.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Publication of this case report and accompanying images was waived from patient's family consent according to the Institutional Review Board of the Children's Hospital of Chongqing Medical University.

International multidisciplinary team (iMDT) discussion

Discussion from Department of Pediatric Surgical Oncology, Children's Hospital of Chongqing Medical University

RCCs are currently thought to account for about 2%

to 4% of kidney tumors in children (11,12), and MiT-RCCs, 93.2% of which are *TFE3* MiT-RCCs, constitute approximately 41.5% of all RCCs, and the age of patients with MIT-RCCs tends to range from 0 to 20 years (13), and there is no standardized treatment for this disease. The main treatment options include surgery, anti-VEGF/VEGFR or VEGFR therapy, mTOR inhibitors, immunotherapy, MET signaling pathway targeting, and chemotherapy (1).

A 2010 retrospective study from France (14) showed that of 21 cases of metastatic Xp11 translocation RCC, 11 patients were treated with sunitinib and nine with cytokines, with sunitinib appearing to be more effective than cytokine administration. A 2016 study showed that for patients with non-clear cell RCC (nccRCC) including advanced papillary, chromophobe, collecting duct carcinoma (CDC), and Xp11.2 translocation, unclassified RCC, and clear cell RCC (ccRCC) with >20% sarcomatoid features, everolimus is not superior to sunitinib (15). In addition, pembrolizumab monotherapy provides long-lasting antitumor activity for previously untreated patients with nccRCC (16). A 2018 study similarly demonstrated the antitumor activity of PD-1 and programmed death-ligand 1 (PD-L1) inhibitors in nccRCC (17).

Here, we report a case with a primary diagnosis of metastatic *TFE3* MiT-RCC. In the patient's overall treatment regimen, we performed a comprehensive and highly individualized treatment that included biopsy surgery, radical nephrectomy for renal carcinoma, radical tumor resection with vascular osteotomy, cervical and thoracic lymph node dissection, sintilimab administration, TKIs targeting VEGFR (from pazopanib to sunitinib), and chemotherapy (neoadjuvant chemotherapy and postoperative chemotherapy), but unfortunately the patient responded poorly to the aggressive treatments and eventually died.

Although the patient's TMB and microsatellite instability analysis results suggested limited potential benefit from immune checkpoint inhibitor monotherapy, it has now been shown that translocation RCC contain a considerable density of tumor-infiltrating CD8⁺ T cells (18), which are susceptible to immune modulation, and the treatment of immune checkpoint inhibition (ICI) makes theoretical sense. However, toward the later stage of treatment, the patient developed a significant amount of bloody ascites. Ultrasound indicated no obvious signs of tumor recurrence at the primary site, but liver metastases were detected. However, it was unclear whether extensive micrometastases

were present within the peritoneal cavity, as the liver function did not show significant abnormalities at that time. Unfortunately, the family of the patient had a limited willingness to pursue further treatment, and regrettably, the patient exhibited a poor response to aggressive therapy, ultimately resulting in death.

There are several definitive diagnostic tools available for *TFE3* MiT-RCCs, including *TFE3* immunohistochemistry, next-generation sequencing (NGS), RNA, and exome sequencing, and *TFE3*-isolated FISH is the gold standard for diagnosis.

With the advancement of immunotherapy in the first-line treatment of metastatic RCC (19), there has been an increased focus on combination therapies, as evidence by the ongoing NCT03595124 and NCT04704219 trials. Therefore, for the treatment of metastatic *TFE3* MiT-RCC, in addition to complete surgical resection at the primary site, early initiation of immunotherapy and the use of precision-targeted drugs are necessary. There is an urgent need for the development of novel immunotherapeutic and targeted therapeutic agents to effectively treat pediatric patients with this condition. Furthermore, additionally research on tumor driver genes and other aspects will be crucial to enhancing the level of precision treatment.

Opinions from the international experts on questions related to diagnosis and treatment of this patient

Q1: What other therapeutic strategies are currently available for the advanced metastatic *TFE3* MiT-RCC reported in this study?

Expert opinion 1: Dr. Fumibiko Urabe

Performing nephrectomy prior to chemotherapy might be an option.

Expert opinion 2: Dr. Mauricio Burotto

These translocation RCC looks like to have tumor-infiltrating CD8⁺ T cells. Which potentially made them hot tumor and susceptible to respond to immuno-modulation. Expert opinion rational and case reports support my suggestion of combine ICI (Ipi-Nivo) or clinical trial with some kind of immune-oncology (IO) in case like this or in general case of *TFE3* MiT-RCC.

Expert opinion 3: Dr. Sebastiano Buti & Dr. Giulia Claire Giudice

All the TKIs and the combination treatment options accessible nowadays for the treatment of RCC have been primarily studied in patients with clear-cell RCC, with limited evidence for MiT-RCC. In fact, randomized trials

addressing this rare entity are not been held, there is not a defined standard of care treatment and the main evidence comes from retrospective analysis or a few phase II trials.

The International Society of Pediatric Oncology (SIOP) recommends the use of preoperative chemotherapy for the localized RCC, with combination regimes of vincristine and actinomycin-D or epirubicin or doxorubicin (20).

For the advanced disease approach, the European Association of Urology guidelines suggest treatments with temsirolimus, everolimus, sorafenib, sunitinib, cabozantinib and pembrolizumab (21), while the National Comprehensive Cancer Network (NCCN) guidelines (22) underline the importance of enrollment in clinical trials, as the preferred strategy, suggesting TKI (cabozantinib, sunitinib, lenvatinib, axitinib, pazopanib), mTOR inhibitors (everolimus, temsirolimus), VEGFR inhibitors (bevacizumab) or ICI (nivolumab, pembrolizumab), either as monotherapy or combination, in alternative.

Regarding more specifically MiT-RCC, evidence is scarce. According to retrospective analysis by the group of Hirsch *et al.* on 52 and 17 patients with metastatic MiT-RCC (9), cabozantinib seemed to provide benefit, either in first- or later-lines, with an objective response rate (ORR) of 17.3% and 29%, respectively. Thouvenin and colleagues reported a median progression-free survival (mPFS) of 6.8 months and a median overall survival (mOS) of 18.3 months (23), while Martínez Chanzá *et al.* collected a median time to treatment failure (mTTF) of 8.3 months and a 1-year OS of 69% (24). Additional evidence comes from the subanalysis of the phase II CaboSun trial, aimed at comparing cabozantinib and sunitinib. Only three patients with MiT-RCC were included and treated with cabozantinib, showing an ORR of 50% and a mPFS of 14 months.

Consequently, cabozantinib could represent a treatment of choice for patients with MiT-RCC, strengthened by the confirmation of MET mutation role in the pathway of MiT (25).

Similarly, pre-clinical study supposed that the secondary resistance to sunitinib may be due to an up-regulation of PD-L1 by TFE3 (26). Consequently, sunitinib may not be the TKI of choice in the treatment of MiT-RCC, with respect to other TKIs.

For instance, the effectiveness of pazopanib was highlighted in a meta-analysis on 15 retrospective or prospective trials on patients with nccRCC, including MiT-RCC. Pazopanib seemed to show good effectiveness in this population, in terms of ORR (range, 27–33%), DCR (range, 81–89%), mPFS (range, 8.1–16.5 months) and mOS (range,

17.3–31.0 months) (27).

Alternatively, axitinib may be a preference, based on the data of a phase II trial on 40 pre-treated patients with metastatic nccRCC receiving axitinib. The subgroup of patients with MiT-RCC (17.5% of the population) seemed to especially benefit from the treatment, with an ORR of 57.1%, a disease control rate (DCR) of 85.7%, a mPFS of 11.1 months and a mOS of 16.9 months (28).

mTOR inhibitors, such as everolimus, may be a good option. Even though the randomized phase II trial, ESPN, failed to show superiority of everolimus over sunitinib, the subgroup of seven patients with MiT-RCC showed mPFS and mOS of 6.1 and 16.2 months with sunitinib and 3 and 8.1 months with everolimus, respectively (15). In addition, data from retrospective analysis may suggest some benefit from a treatment with mTOR inhibitors (14).

Preclinical data also strengthen the importance of the PI3K/AKT/mTOR pathway in MiT-RCC (29).

Regarding ICIs or ICI + TKI combinations, the phase II KEYNOTE-B61 trial evaluated a first-line therapy with lenvatinib + pembrolizumab in patients nccRCC, including six with MiT-RCC, showing an ORR of 67%; similarly, the phase II CaboNivo trial evaluated a first- or second-line therapy with cabozantinib + nivolumab in patients nccRCC, including two with MiT-RCC, showing an ORR of 50% and a mPFS of 14 months. Lastly, a phase II trial of atezolizumab and bevacizumab for patients with metastatic nccRCC enrolled five patients with MiT-RCC, with an ORR of 20% (30). Some additional data may be derived from retrospective analysis. The group of Alhalabi *et al.* highlighted a scarce response to a dual ICIs treatment on 29 patients affected by MiT-RCC, with an ORR, a mPFS and a mOS of 5%, 2.8 and 17.8 months, respectively; patients seemed to benefit from a combination therapy with ICI and TKI, instead, with an ORR, a mPFS and a mOS of 36%, 5.4 and 30.7 months, respectively (31). In a retrospective analysis of 22 patients with MiT-RCC, an ICI treatment seemed to benefit a higher ORR and longer OS, compared to TKI (ORR 25.0% *vs.* 0%, OS 62.4 *vs.* 10.3 months, respectively) (18). Lastly, a real-world data report on patients affected by nccRCC, included nine patients with MiT-RCC receiving systemic treatment; 44.4% of patients received sunitinib while 55.6% ICI + TKI combination. Patients receiving an ICI treatment seemed to show the major benefit with an ORR of 40% and a median PFS of 7.3 months. Sadly, no patient was still alive after 5 years (32).

Considering all the available evidence, a treatment with

a combination of ICI and TKI may be of choice in the current treatment of patients with MiT-RCC.

Q2: What should be the timing of the application of targeted agents (e.g., VEGFR-TKI) for cases such as this one?

Expert opinion 1: Dr. Fumihiko Urabe

This timing is the best.

Expert opinion 2: Dr. Mauricio Burotto

I would suggest IO-IO combination in first line, maybe a regime like the COSMIC-313.

IO-IO-TKI could be an option in this subtype of RCC. Would be my first choice in clinical practice.

Expert opinion 3: Dr. Sebastiano Buti & Dr. Giulia Claire Giudice

The nowadays available data are not sufficient enough to define an adequate sequence strategy, although TKIs could be a wise choice in first-line treatment, given the acceptable toxicity for hopefully a long duration of treatment. Particularly, in a retrospective study, cabozantinib seemed to show better benefit when administered in first-line than in later-lines (mPFS of 6.8, 11.7 months for first-line, 6.5 months in later-lines) (23).

Q3: Late in the course of treatment, the patient developed a large amount of ascites in which tumor cells were visible, but imaging suggested no *in situ* recurrence and the patient's protein levels were relatively normal: what should be considered the typical cause of this situation?

Expert opinion 1: Dr. Fumihiko Urabe

This mechanism is very difficult.

Expert opinion 2: Dr. Mauricio Burotto

Because of the poor prognostic and aggressive clinical presentation, a peritoneal compromise is not particularly rare. I am treated patient with pleural compromise and lymphangitis and retroperitoneal compromise very aggressive.

Expert opinion 3: Dr. Sebastiano Buti & Dr. Giulia Claire Giudice

In case of ascites onset, every differential cause should be excluded. Taking into account all conditions of ascites, including heart failure, hepatic failure, nephrotic syndrome, pancreatitis, hypothyroidism, venous alterations, amyloidosis, constrictive pericarditis and infections, comprehensive blood and urine tests and heart and abdomen ultrasound evaluations may be performed. Additional instrumental exams may be carried out, such

as CT scans, being aware that sensitivity and specificity for detecting peritoneal metastasis seemed to be 68% and 88%, according to a meta-analysis on 37 studies, while magnetic resonance imaging (MRI) may be the exam of choice, with higher sensitivity and specificity (92% and 85% respectively) (33). Lastly an ascitic fluid examination, including biochemical and smear, may clear the diagnosis.

In addition, it is worth remembering that, rarely, TKI may be a cause of nephrotic syndrome, with or without associated proteinuria (34,35).

Lastly, malignant ascites, without visible large mass or other distant metastases, has been reported to be a very rare presentation of RCC (36,37).

Conclusions

Based on this case report of advanced metastatic TFE3 MiT-RCC and other studies, we believe that early molecular diagnosis with genetic testing is necessary for treating advanced, multimetastatic TFE3 MiT-RCC and that the early use of immunotherapy and targeted therapies may be beneficial. Novel targeted drugs and therapeutic strategies are still needed to improve the outcome of patients with metastatic TFE3 MiT-RCC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Publication of this case report and accompanying images was waived from patient's family consent according to the Institutional Review Board of the Children's Hospital of Chongqing Medical University.

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