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Getting to a Diagnosis: A Rare Case of TFE3 Translocation Renal Cell Carcinoma in a 22-Year-Old Male

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Abstract

Primary renal cell carcinoma (RCC) with metastasis is common with an estimated 30% of patients with RCC having metastases at the time of diagnosis. Evidence of metastatic RCC without a primary renal tumor is extremely rare with only a handful of cases citing this occurrence. Occasionally an unclear patient presentation requires thoughtful consideration of all the possibilities and results in a clinician reexamining the data to expand a differential, thus arriving at a diagnosis. This is the case of a 22-year-old who presented with diffuse lymphadenopathy, fever, cough, lower abdominal pain following a trip to India where the patient was hospitalized, initially believed to be tuberculosis. After multiple needle biopsies of lymph nodes and a retroperitoneal mass that were insufficient for a diagnosis, a wide excisional biopsy was performed that led to a diagnosis in our patient. The patient was diagnosed with metastatic TFE3-rearranged (MiT translocation) renal cell carcinoma and subsequently started on pembrolizumab and Lenvatinib followed by debulking surgery.

Keywords

Renal Cell Carcinoma, Metastatic, Retroperitoneal Mass, Tuberculosis, Primary Tumor

1. Introduction

According to the most recent data from Surveillance Epidemiology and End Results, kidney and renal pelvis cancer accounts for 4.2% of all cancer cases and 2.4% of all cancer deaths [1]. The presentation of primary renal cell carcinoma (RCC) with metastasis is common. It is estimated that around 30% of patients with RCC

have metastases at the time of diagnosis [2] [3]. The prognosis of metastatic RCC is not favorable, with a 5-year survival rate for stage IV metastatic disease to be about 17.4% [1]. Common metastatic sites for RCC include lung, bone, lymph nodes, liver, adrenal, and brain [4]. Evidence of metastatic RCC without a primary renal tumor is extremely rare with only a handful of cases citing this occurrence [5]-[8]. A rare and aggressive type of RCC is translocation RCC that is associated with genetic rearrangements of TFE3 gene on chromosome Xp11.2 [9]. Unfortunately, the underlying molecular genetics of TFE3 translocation RCC are not well understood. A reason for this is that the TFE3 gene has been documented to have more than 20 different partner genes that it fuses with and the large number of diverse fusions leads to a high degree of heterogeneity in terms of functionality of the TFE3 fusion proteins that are produced. This large number of genetic partners could explain why some TFE3 translocation RCCs express high levels of PD-L1 while others express low levels of PD-L1. There is no universally accepted optimal therapy for TFE3 translocation RCC due to the varying expression of immune checkpoint regulators [10]. Alas, the TFE3 translocation variant of RCC still affects a good number of patients. For example, a specific MiTF/TFE translocation is associated with being involved in 40% of all pediatric and adolescent RCCs and 1% - 4% of all adult RCCs [2]. We present a rare case of metastatic TFE3 translocation RCC in an adult male with no evidence of a primary renal tumor.

2. Case Presentation

A 22-year-old presents with 2 weeks duration of abdominal pain, cough, fever, arthralgias and a recent trip to India presented to the emergency department. During the trip in India, the patient was residing in an endemic area and was hospitalized for a sickness similar in presentation to the one above and imaging was performed that demonstrated necrotizing lymphadenopathy, raising concerns for tuberculosis. Tuberculosis was the initial first suspected etiology for the patient's disease due to the travel to an endemic area and the short period of symptoms that leaned towards an infectious etiology as explanation for the acute onset of illness. Upon questioning in the emergency room, the patient had endorsed no past medical history. Surgical history included adenoidectomy as a child. Family history of essential hypertension in the patient's father, miscarriages in the patient's mother, a paternal great aunt with a history of breast cancer. There was no notable history for renal cell carcinoma. The patient had no history of tobacco, alcohol, or illicit substances. At the time of presentation, the patient was afebrile and in no apparent distress. The abdomen was soft, with a left, lower quadrant tenderness. The left flank demonstrated paraspinal tenderness and there were palpable left supraclavicular lymph nodes. Oxygen saturation was 97% on room air. The remainder of the physical exam was unremarkable. With the patient's recent travel and imaging demonstrating necrotic lymphadenopathy the patient was placed in airborne precautions to rule out tuberculosis.

2.1. Investigations

In the emergency room, lab work was drawn and showed a hemoglobin of 12.1 (13.5 - 16.5 gm/dl) and sodium of 135 (137 - 147 mmol/L). Chest X-ray demonstrated small ovoid opacity over the left lower mediastinum, interpreted as a small hiatal hernia or lymphadenopathy. Initial acid-fast microscopy and nucleic acid amplification test (NAAT) of sputum on day of admission came back negative, and sputum culture was started to further evaluate. On the third day of admission, Chest CT was performed given travel to endemic TB area and demonstrated partially cystic posterior mediastinal, retro crural, and left supraclavicular lymphadenopathy. Based on the findings and reading from radiologist of the scan, the differential diagnoses were tuberculosis versus metastatic versus hematological etiology for this lymphadenopathy (Figure 1).

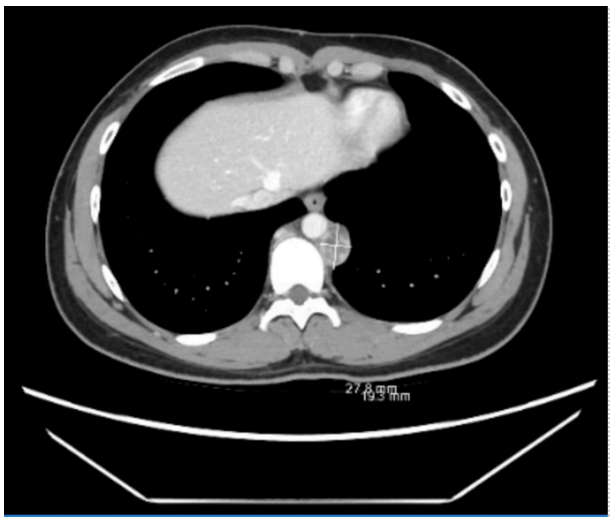


Figure 1. CT Chest: Representative left posterior mediastinal lymph node measuring 2.8 × 1.9 cm.

Peripheral blood flow cytometry was performed after consulting hematology service for concern of lymphadenopathy being of hematological origin and did not express immunophenotypic evidence of non-Hodgkin lymphoma. On 5th day of admission, a CT abdomen and pelvis with contrast was performed given the patient LLQ pain on presentation and demonstrated a large, thick walled, predominantly cystic left retroperitoneal mass. The mass displaced, though did not appear to arise directly from the pancreas, left kidney, or adrenal gland. There was partial vascular encasement and displacement of the aorta. The primary consideration was that the lymphadenopathy was necrotic given associated cystic retroperitoneal and thoracic lymphadenopathy. There was a consideration on the report by the radiologist that based on the CT of the abdomen and pelvis the differential diagnosis was metastatic disease from primary scrotal malignancy versus retroperitoneal sarcoma or germ cell tumor were read as a consideration (Figure 2).

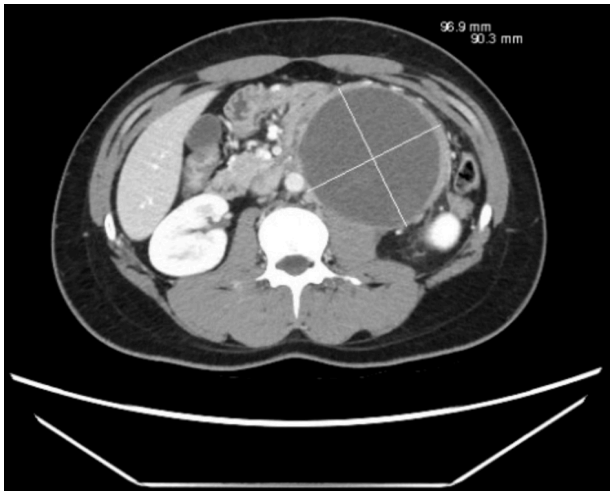


Figure 2. CT Abdomen and Pelvis with contrast: large cystic mass arising from the left retroperitoneum measuring 9.7 × 9 cm.

Due to the patient's age, a scrotal ultrasound was obtained and was normal. Other lab work done at this time included beta-hCG, uric acid, LDH, HIV, toxoplasmosis, syphilis, and bartonella to investigate other infectious/malignant causes and all results were negative. On the 7th day of admission, a biopsy of the left supraclavicular node and abdominal mass was performed to try to get a tissue sample for pathological diagnosis of disease. The procedure did not yield enough tissue of lymph node to make a diagnosis, but abdominal fluid was able to be aspirated from the abdominal cystic lesion and showed macrophages and debris consistent with cystic contents. Given possible cancer etiology and having not been able to rule out tuberculosis as etiology of disease yet because culture was still in process, a PET scan was performed on 12/27 and showed large left retroperitoneal abdominal mass with mild peripheral hypermetabolism (maximum SUV of 5.3). The remainder of previously described partially necrotic lymphadenopathy demonstrated low-grade uptake. Small hypermetabolic upper cervical and left hilar lymph nodes showed signs that they may be reactive (**Figure 3**).

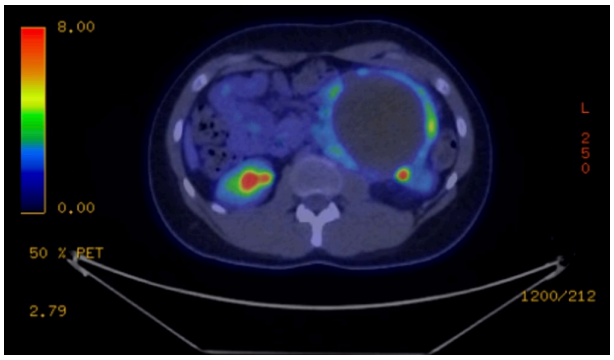
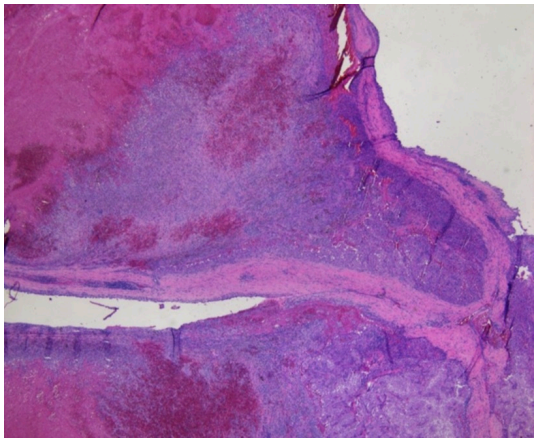
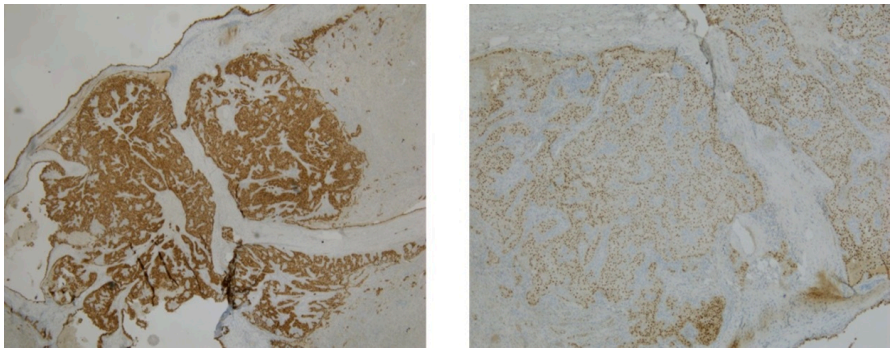


Figure 3. PET scan: Large left retroperitoneal abdominal mass with mild peripheral hypermetabolism. The remainder of the previously described partially necrotic lymphadenopathy demonstrates low-grade uptake.

On 17th day of admission, the sputum sample culture was still in process, the PET scan was concerning for malignancy, and that there was no etiology for the disease process yet, it was decided as a team that it would be best to try for a repeat biopsy of the retroperitoneal mass with a skinny needle biopsy as well as a core biospy. The biopsy yielded 193 mL of black fluid from the abdominal cystic lesion. The material was insufficient for flow cytometry study. Furthermore, the ultrasound-guided retroperitoneal mass core biopsy was performed and analysis showed that it was positive for TFE3 and PAX8 on staining but ultimately did not show any signs of malignancy. The pathologist interpreted the biopsy as being non-diagnostic scant chronic inflammation, fibrosis and fibrinoid material (**Figure 4**).



(a)



(b)

Figure 4. Retroperitoneal Mass Biopsy: Diffusely positive TFE3 (left) and PAX8 (right) stains. Histology showed the specimen is composed of scant soft tissue which has mild fibrosis as well as some fibrinoid material. There is a focus of chronic inflammation, which does not show atypia and there are about 10 epithelial cells on the edge of the tissue, which might represent mesothelial cells, or even a minute cyst wall lining. Also, the histological interpretation showed no evidence of granulomata, acute inflammation or malignancy.

Due to not being able to find an etiology after multiple failed conservative biopsies and the sputum culture for tuberculosis still being in process, it was decided to move forward with an excisional biopsy of a left neck lymph node a week later

on the 22nd day of admission. This biopsy resulted with the diagnosis of metastatic TFE-3 rearranged renal cell carcinoma on pathological examination (Figure 5).

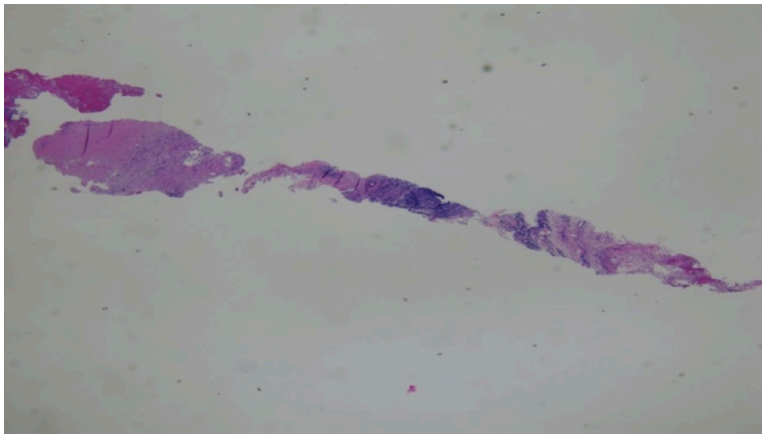


Figure 5. Lymph node left neck: Diffusely positive for PAX-8 and TFE3, show patchy strong staining with pancytokeratin and CK7, and have partial nonspecific nuclear WT-1 and retained INI-1. Negative for CK20, TTF-1, calretinin, SALL-4, glypican-3, GATA3, p40, mammaglobin, S-100, AR, ALK-1, and special stain mucicarmine. Findings support the diagnosis of Metastatic TFE3-rearranged renal cell carcinoma.

2.2. Outcome and Follow-Up

The case was presented at tumor board and retroperitoneal lymph node dissection was performed, followed by left supraclavicular and left mediastinal lymph node dissection, which all confirmed the diagnosis. Lenvatinib 14 mg daily and cycles of Pembrolizumab 100 mg IV every 21 days was the treatment plan that was initiated around a month after diagnosis and pt was referred to medical oncology for ongoing treatment. The patient had an excellent response to therapy with CT scans showing a decreased size of the posterior mediastinal and retrocrural lymphadenopathy as well as the retroperitoneal mass and lymph nodes after only 3 months of therapy. Repeat CT scans 6 months after initiating treatment showed stable disease. At 18 months after diagnosis, the patient underwent a retroperitoneal lymph node dissection and at 21 months after diagnosis, the patient underwent a left supraclavicular mediastinal lymph node dissection. There was a tentative plan to perform right sided retrocrural lymph node and right mediastinal lymph node dissection 22 months after diagnosis, but the patient had imaging performed at the time that demonstrating recurrence of disease. The patient had been off levatinib to facilitate wound healing after debulking surgeries but was restarted on Lenvatinib after disease recurrence. The patient's current chemotherapy regimen is levatinib 28 mg and pembrolizumab 200 mg IV every 21 days. The patient recently received a 26th cycle of pembrolizumab. Most recent imaging performed 24 months after diagnosis shows stable disease. There are no signs of cancer resistance based on treatment response and surveillance. The patient is still living and able to carry out daily activities of life including work and school.

3. Discussion

An infectious etiology was initially considered due to our patient's acute presentation of high fever, chills, arthralgia with nonproductive cough, and more specifically tuberculosis due to recent travel to an area that was endemic for tuberculosis. The initial studies of microscopy and NAAT being negative did not support the diagnosis of tuberculosis, but these tests do not have the best sensitivity, and we wanted to wait for the results of the sputum culture before truly ruling out tuberculosis. We might have discharged the patient home if there had not been concern for extrapulmonary tuberculosis versus malignancy based on interpretation of initial CT scans of chest and abdomen/pelvis. Our primary goal was to get some sort of patient tissue that could be pathologically examined before discharging the patient given the importance of diagnosing metastatic cancer as soon as possible if that is what the etiology of the disease turned out to be. This thought process led us to perform multiple core biopsies of both the lymph nodes and the retroperitoneal mass. Unfortunately, all of these procedures lacked definitive diagnosis due to insufficient tissue retrieved from biopsies. After multiple failed attempts and a PET scan that showed peripheral hypermetabolism of the left retroperitoneal mass on PET scan further supporting malignancy, there was a long discussion between the different care teams of the risk on benefits of trying to continue to perform core biopsies versus going with a more aggressive approach of a wide excisional biopsy. We decided it was best to move forward with a wide excisional biopsy because it would most likely provide us with enough tissue to make a diagnosis as well as decrease the potential that the patient would have to receive more procedures before understanding what their actual disease they have is. This combination of beneficence and wanting to get answers for the patient and their family led us to perform a wide excisional biopsy of the left supraclavicular node to increase tissue yield for histological evaluation. The pathological examination of the wide excisional biopsy gave us a definitive diagnosis of metastatic RCC.

Initially, neoplastic etiology was lower on the differential diagnosis because of the patient's symptoms, course of disease, and recent travel pointed more towards infectious etiology. Furthermore, metastatic RCC was not in the initial differential of our patient because of the lack of signs and symptoms in typical metastatic sites of RCC. Unlike our patient, RCC does not typically metastasize to the retroperitoneal space. For example, in a retrospective analysis of 196 cases of RCC, the most common metastatic sites were lung (31.1%), bone (29.1%), and digestive system (19.4%) [11]. However, this case of RCC was not the first to have retroperitoneal cystic metastases. Rastogi and Ishii *et al.* both reported RCC with cystic retroperitoneal nodal metastases [12] [13]. In addition to the retroperitoneal space, other cases have reported unusual metastatic sites for RCC including the breast, pancreas, scalp (cutaneous), jaw, forearm, parotid, skeletal muscle, etc. [14]-[17]. These studies provide further support that our patient's presentation is uncommon.

Another rarity in our patient was the lack of a primary renal mass on imaging.

The presentation of metastatic RCC without a primary renal tumor is an uncommon phenomenon with only a handful of cases reporting the occurrence [5]-[8]. The mechanism behind this phenomenon is unknown with only a few explanations present. These explanations are described best in a case series study published in Current Oncology in June 2014. The explanations included the possibility of spontaneous regression of a once primary tumor, the development of RCC occurred in ectopic tissue, and that the renal mass is too small to detect whether enhancement is present [5]. The last theory most likely explains our patient's presentation due to the TFE3 translocation present in the genetic makeup of their disease. Our patient most likely has primary renal mass(es) that are too small to be seen on imaging based on the knowledge that TFE3 translocation RCC in adults often shows an aggressive clinical course [18]. For example, a case series by Meyer *et al.* described a median survival time of 18 months for 5 adults with TFE3/Xp11.2 translocations [19]. These studies point to an aggressive disease course, as in our patients. Based on this knowledge, our patient was quickly initiated on a treatment regimen.

There is not a current standard initial treatment for TFE3 translocation RCC due to the rarity of this disease. Previous observational studies have shown some efficacy with anti-VEGF antibodies, such as sunitinib, in treating the disease [20]. The results of the recent KEYNOTE-B61 phase II trial support the use of pembrolizumab plus Lenvatinib as first line treatment for patients with advanced non-clear-cell RCC [21]. Based on the patient's malignant presentation and recent findings of the KEYNOTE-B61 trial, the oncologist in charge of our patient's care thought that a treatment regimen of pembrolizumab plus Lenvatinib would provide the most benefit to our patient. Challenges that are faced during treatment with this treatment combination are the delayed wound healing that is present with Lenvatinib. This makes it difficult to decide whether to prioritize continuing chemotherapy over pursuing tumor debulking surgery. We saw this firsthand with our patient, when they were off Lenvatinib for debulking surgery, the cancer had a recurrence. This is not to say that this will happen in every patient, but more of a point to be made that more studies, including observational and possibly clinical trials that look at what treatment modalities are best for aggressive variants of RCC. There is a tough clinical decision to make on treatment for metastatic non-clear-cell RCC given the prognosis of it and further research is needed to establish proper treatment guidelines for these patients in terms of using continuous chemotherapy versus debulking surgery versus a combination of the two treatment modalities.

4. Conclusion

In conclusion, this case report adds to our collective knowledge of the unusual way in which metastatic TFE3 translocation RCC can present. The prognosis of metastatic TFE3 translocation RCC in adults is poor and management of the disease has not been well defined due to the rarity of the disease. However, physicians

must remain vigilant in diagnosing metastatic RCC to ensure swift initiation of treatment. The use of CT scans can help to characterize unknown retroperitoneal masses as well as necrotic lymph nodes; however, diagnosis can only be achieved through biopsy. When evaluating retroperitoneal masses and necrotic lymph nodes, metastatic RCC should be considered even in the absence of a primary renal mass.

Consent

Informed consent was obtained from the patient to report this case.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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