Acta Scientific Clinical Case Reports

Volume 4 Issue 9 September 2023

Case Report

Diagnosis and Management of Rare Case of Locally Advanced Non-Clear Renal-Cell Carcinoma: A Case Report

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Received: August 11, 2023

Published: August 17, 2023

Abstract

Introduction: Non-clear cell renal carcinoma is one of the rarest malignancy subtypes in RCC (Renal Cell Carcinoma), with no specialized treatment. In this case report, the chemotherapeutic drugs carboplatin and paclitaxel were reviewed and studied for the treatment of a rare tumor that was high grade, poorly differentiated, unclassified non-clear renal cell carcinoma (RCC) of locally advanced stage with active disease post-operatively.

A 23-years-old woman was diagnosed with locally advanced, high grade, poorly differentiated, unclassified non-clear renal cell carcinoma (RCC) with difficulty, and this case report will discuss chemotherapy treatment options in non-clear RCC locally advanced (stage III) with the use of carboplatin and paclitaxel for 6 cycles every 21 days and its role and impact on tumor response, general clinical condition, and prognosis.

Results: After receiving 6 cycles of chemotherapy (carboplatin and paclitaxel) as adjuvant therapy following total radical left nephrectomy for this patient with locally advanced unclassified undifferentiated Non-Clear RCC and active pelvic lymph node metastases post-operatively, there was complete disease response with a total absence for this active lymph node by follow-up PET scan. The patient in addition had a dramatic clinical response, going 3 years without any evidence of disease recurrence.

Conclusion: Patients with unusual displays of locally advanced, unclassified, poorly differentiated Non-Clear Renal Cell Carcinoma (nccRCC) after radical nephrectomy had complete tumor responses to chemotherapy carboplatin and paclitaxel as adjuvant treatment for 6 cycles with reduced toxicity profiles, indicating that this treatment option can be used for this highly unusual tumor type.

Keywords: nccRCC (Non-clear renal cell carcinoma); IHC (Immune Histochemistry); MRI (Magnetic Resonant Imaging); PET scan (Positron Emission Tomography)

Introduction

Recent developments in the treatment of locally and regionally progressed clear renal cell carcinoma (ccRCC) have been numerous [1].

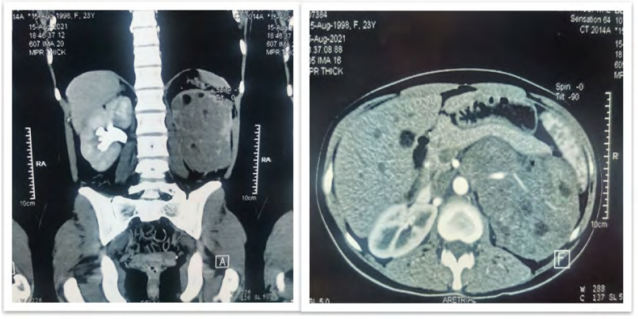
The bulk of these studies, however, did not include patients with Non-Clear RCC (nccRCC), therefore the most effective way to treat nccRCC is still uncertain [2]. The non-clear RCC group, which is divided into various subtypes with unique genetic and biochemical traits, is made up of a number of uncommon and poorly understood

disorders. A standard of care has not yet been defined, and treatment decisions are dependent on extrapolating findings from clear cell RCC trials, retrospective data, or case reports [3].

Case Presentation

A 23-years-old lady presented to the clinic with a previous history of recurrent left loin and epigastric pain for 4 months duration with loss of weight, decreased appetite, her pain increased in severity by time then developed frank hematurea on which patient visited the GP (general practitioner) who sent her GUE (general urine examination) and abdominal ultrasound, incidentally he found that the patient had a suspected left renal mass.

Then CT scan of the abdomen and pelvis was done for her showing: a big left renal mass 16cm x 12.5cm x 9cm in size originating from and involving all renal parenchyma, invading the renal capsule extending medially slightly crossing the midline and partially surrounding left side of aorta, totally encasing the left renal artery and its main branches pressing left renal vein anteriorly, pushing pancreas and stomach and bowel loops anteriorly, mildly enlarged regional L.Ns seen medially to the mass, suggesting of aggressive renal tumor (lymphoma considered more likely differential as the kidney diffusely involved, less likely differential RCC which is more localized.



Figures 1 and 2: Respectively display left renal mass 16cm x 12.5cm x 9cm in size involving all renal parenchyma, extending medially, and shifting the midline and encasing renal artery and vein to left side of aorta, reaching pancreas and stomach.

LHer GP referred her to a urologist surgeon on which he planned to do a total radical nephrectomy for her.

Operation was done with total resection of the mass and regional L.N. dissection with negative margin and biopsy revealed 16 x 12.5cm left renal mass with a possibility of Wilms tumor diagnosis stage (T4N0Mx) as shown is figure 3.

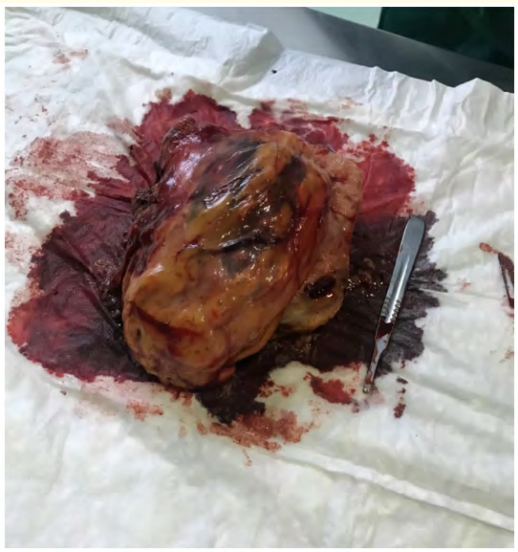


Figure 3: Shows left renal mass 16cm x 12.5cm.

Then the patient was referred to the researcher (oncologist) whom she did thorough clinical evaluation by clinical examination, the patient has negative family history of renal cell carcinoma (RCC) or any malignancy, negative personal history of ca, also was sent for complete blood examination including CBC, liver function test, renal function test, with a complete metabolic panel and staging CT chest plus MRI of the whole spine. Staging CT scan revealed no residual at the site of operation with negative lymph node and no distant metastasis.

Then IHC (immunohistochemistry) was sent on this biopsy sample and revealed: multifocal renal parenchymal infiltration by a triphasic tumor, mostly featuring sheets of round blue cells (blastemal component) together with stromal component composed of spindle cells and the least is epithelial cells, negative resection margin, negative 6 resected lymph node goes with stage III Wilms tumor.

Second review biopsy was sent to a second different lab because of the rarity of Wilms tumor incidence in this age group and

biopsy revealed: the diagnosis of non-clear renal cell carcinoma, undifferentiated of unclassified histology. Immunohistochemistry (IHC) on this biopsy sample showed: E1/3: diffuse and moderately positive, PAX-8: negative, CD10: negative, CK7: negative, CK20: negative, CD56: focal and weak staining mostly negative, vimentin: focal and weak staining, WT-1: negative, neither conclusive histologic nor IHC feature to suggest Wilms tumor or conventional (clear) RCC.

Because of these 2 different results in 2 biopsy reviews, a third review of the diagnosis in a third different lab revealing: the "possibility" of the diagnosis of undifferentiated RCC although Wilms tumor can't be excluded. The histopathology showing high grade malignant neoplasm made up of solid sheets of hyperchromatic atypical cells with no obvious differentiating lines.

IHC staining shows

WT-1: negative, and negative CD10, PAX-8, CK7, CK20, and vimentin with focal positivity of CD56, AE1/3, focal positivity for EMA and negative for desmin.

The diagnosis was still confusing between Wilms tumor and unclassified RCC, so a fourth review of biopsy sample was done in a fourth different lab and results showing: the possibility of non-clear RCC and undifferentiated type, high grade tumor, invades perinephric and renal sinus fat, LVI positive for lymph-vessels only, 6 L.Ns negative for metastasis, stage T3aN0Mx description tumor composed of solid sheets of poorly differentiated cells, having hyperchromatic nuclei, little cytoplasm with high mitotic rates and foci of comedo like necrosis, these neoplastic cells separated by fibroblastic stroma with foci of focal tubular differentiation, tumor cells infiltrating renal parenchyma, IHC results: positive AE1/AE3 pan cytokeratin and CD56 and focally positive for EMA and PAX-8. Other IHC markers: negative.

The diagnosis is non-clear high-grade adenocarcinoma, the tumor does not fit into any of RCC subtypes: clear cell ca, urothelial ca, translocation associated ca, chromophobe ca, or papillary RCC and it is better to be managed as unclassified RCC high grade.

Due to this tumor's rarity and the conflicting biopsy results and after discussion with meeting committee, a restaging PET scan (positron emission tomography) was ordered showing 1 FDG-avid active regional pelvic LAP with SUV max = 12.5, confirming metastatic regional lymphadenopathy post operatively.

After discussion for the second time with the oncology meeting committee of this type of tumor and PET scan results, chemotherapy was planned to be given with carboplatin and paclitaxel for 6 consecutive cycles as adjuvant therapy every 21 days cycle, the treatment well-tolerated with excellent performance status with no mentionable side-effects.

A follow-up PET scan post chemotherapy was done and showed complete radiological response, no regional LAP was seen, no distant metastasis with clear surgical bed. According to these final results, patient was planned to be on active surveillance every 3 months for the first 2 years and complete response was achieved.

Till now, patient is on thorough clinical observation by clinical examination, blood investigation, and periodic evaluation by CT scan with complete response and no disease recurrence with normal blood urea and serum creatinine, performance status=0, completely asymptomatic as it is shown in figure 4.

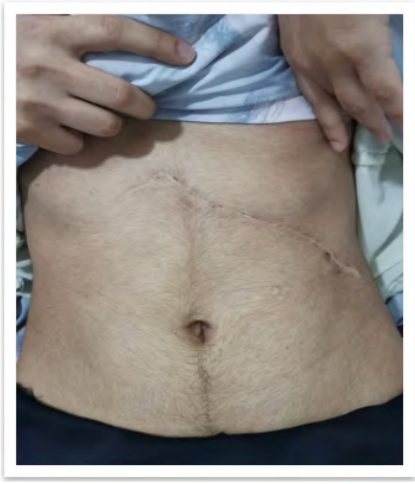


Figure 4: Displays patient post operatively with normal, clear operation site, and scar with good performance status.

Discussion and Literature Review

The term "non-clear cell Renal Cell Carcinoma" (nccRCC) refers to an array of uncommon, poorly understood ailments that

frequently have poor prognosis and no accepted standard of care. When treating nccRCC with non-tailored medicines, the gap in their clinical care is related to the inadequate molecular characterization of the disease [1]. Non-clear RCCs are marginalized in prospective randomized studies as a result of their rarity. Therefore, decisions regarding treatment are made based on extrapolating findings from clear cell studies, archival data, or case reports [4]. There is still a lack of overall data to support the best therapeutic approach for individuals with locally progressed or metastatic nccRCC, and many questions remain unresolved. To our knowledge, systematic therapy's effectiveness, and side effects for nccRCC have only been compared in one earlier systematic review and meta-analysis [5]. Current clinical practice RCC guidelines from the National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) recommend treatment based on scant evidence, and randomized studies using newer agents are urgently required for this patient population.

Angiogenesis inhibitors, vascular endothelial growth factor receptor inhibitors, other tyrosine kinase inhibitors (TKI), MET inhibitors, and mammalian targeting of rapamycin (MTOR) inhibitors have all been mentioned as mainstay treatments for metastatic RCC (mRCC) over the past 20 years [6].

In this case study, the focus will be on the role of systemic chemotherapy in the management of locally advanced, atypical poorly differentiated unclassified Non-Clear cell renal cell carcinoma (nccRCC) with carboplatin plus paclitaxel in stage III (nRCC) for 6 consecutive cycles as adjuvant treatment post radical nephrectomy with active lymph node (L.N.) postoperatively and with strong similarities to locally advanced Wilms tumor by histopathology and its effect on response rate clinically and by imaging.

The chemotherapy in general, a side from trials, previously was given to the patients with collecting duct histology, there were two studies of traditional chemotherapy: one with carboplatin plus paclitaxel and the second using capecitabine [7,8].

There was just one documented response to the treatment among the 16 patients who got carboplatin and paclitaxel, and this was a complete response (CR) in a patient with collecting duct histology alone.

According to a single arm and prospective study of the expanded access programme in nccRCC, tyrosine kinase inhibitors (TKI), such as sunitinib [9-12], sorafenib, axitinib [13], pazopanib [14] are additional common treatments for this uncommon tumor form.

Everolimus without bevacizumab and more recently immunological check point inhibitors like pembrolizumab have been investigated based on safety and efficacy through the ketone-427 trial for Mammalian Target of Rapamycin Inhibitors (m-TOR) inhibitors.

The most prevalent variety of non-clear cell RCC (nccRCC) based on histology is the papillary type, which tends to be multifocal and bilateral, is diagnosed incidentally, and exhibits less aggressive clinical behavior than its clear cell counterparts [16].

The second type is chromophobe RCC, which accounts 5%-7% of all RCC cases and low malignant with 5%-6% risk metastasis [17]. The third type is collecting duct CA, the diagnosis (Dx) is incidental and in most cases at advanced stages with poor prognosis and liver, lymph node lungs, bones, and adrenal glands are more frequent sites of metastasis [18].

Other type is sacromatoid RCC and is not defined as a distinct entity, it comprises up to 20% of mRCC with high grade aggressive tumors and short survival [19,20].

Other histological types, according to the 2016 WHO classification of urogenital tumors (WHO, blue book) including other renal tumors like unclassified nccRCC, hereditary leiomyomatosis, and p11 translocation RCC, renal medullary cancer [21].

Everolimus and sunitinib were compared in the ESPEN trial in all subtypes of nccRCC (27 papillary, 12 chromophobe, 10 unclassified, 7 translocation, and 12 sarcomatoid), taking into account earlier clinical trials that included therapy choices for unclassified nccRCC ([[22]. Only three partial responses were recorded, all of which were treated with sunitinib in the first line setting and one with everolimus [22]. The ASPEN trial is another study comparing everolimus to sunitinib in all subtypes of nccRCC [23], this study included 70 papillary, 16 chromophobe, 8 translocation, 22 unclassified and 16 sarcomatoid RCC [23].

Overall survival (OS) and progression of survival (PFS) did not show any statistically significant differences. Expletory analysis

of this trial revealed that sunitinib treatment improved (PFS) in individuals with good risk disease [23]. Additionally, varied responses for subtypes were seen, with improved (PFS) in sunitinib-treated patients with papillary and unclassified receiving histology [23].

Despite this limitation, the authors came to the conclusion that sunitinib is well tolerated and has an oncological effect in the group with poor prognosis [24]. including subjects with non-clear histology with similar progression free survival (PFS) similar to clear cell histology [25].

After receiving treatment for vague abdominal pain and weight loss for 4 months, this 23-year-old lady was incidentally found to have a large left renal mass measuring 16cm by 12.5cm in size, originating from left renal parenchyma that had invaded the renal cortex and had spread to the pancreas and stomach, suggesting RCC by CT scan of the abdomen. This patient underwent a total left radial nephrectomy with a negative margin and pelvic lymph node dissection.

It is still unclear how cytoreductive nephrectomy (CN) improves survival, but possible explanations include removing large primary tumors that serve as immunologic sinks for antibodies and tumor reactive lymphocytes, delaying disease progression, and reducing disease burden [26] and reducing the amount of growth factors secreted by the primary tumor [27].

However, given the few systemic treatment options available, vigorous surgical resection appears to provide the patient with locally progressed or metastatic non-clear RCC with the best chance for extended survival currently available [28]. The diagnosis of unclassified poorly differentiated non-clear cell RCC was confirmed following multiple diagnostic challenges and difficulties to distinguish it from primary Wilms tumor by histopathological slides in this case of a 23-year-old lady without a family history of malignancy. The patient had a large left renal mass measuring 16 cm x 12.5 cm that was discovered by an abdominal CT scan, strongly suggesting RCC. A total left radical nephrectomy was performed. Although there were no set protocols in the guidelines for treating this case, an adjuvant chemotherapy trial was conducted using carboplatin in addition to paclitaxel systemic treatment for six cycles, every 21 days; the dose was with AUC 6 and paclitaxel dose 175mg/m^2 every 21 days cycle for locally advanced stage III and with 1 active positive pelvic lymphadenopathy approved (LAP) by PET scan post-operatively with high fluorodeoxyglucose (FDG) -a avid uptake of 12.5. After six cycles of treatment and follow-up, the patient showed a full response, the lymph nodes on the PET scan were entirely negative. Since 2021, there has been no disease recurrence and a treatment well-tolerated with no noticeable side effects.

As a result, it may be concluded that carboplatin and paclitaxel, when administered for 6 cycles as adjuvant therapy for locally advanced non-clear unclassified RCC, can improve both the overall survival (OS) and progression-free survival (PFS) for this extremely rare tumor type.

Conclusion

Non-clear RCC is a heterogeneous assortment of diseases consisting of a number of diverse cancer forms that are categorized by histology but range in their clinical outcomes, presentation, and genetic underpinnings. The results of this trial demonstrated the effectiveness of adjuvant systemic chemotherapy with carboplatin and paclitaxel in treating locally advanced nccRCC with unclassified histology. The treatment resulted in exceptional complete responses and overall survival with a significantly lower reported risk profile in this extremely uncommon tumor form.

Recommendations

- Because nccRCC is uncommon and has poor molecular characterization, it is underrepresented in clinical trials and frequently treated with inappropriate therapies, necessitating the need for greater information on the biology of these histologies.
- To provide a standard of care for these tumors, controlled clinical studies based on biomarkers and collaborative trials specific to histology are now being conducted.

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