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Therapeutic approach guided by genetic alteration: Use of MTOR inhibitor in renal medullary carcinoma with loss of PTEN expression

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Renal Medullary Cancer (RMC) is a rare and aggressive type of renal cell cancer that presents predominantly in patients with sickle cell hemoglobinopathies, and is typically metastatic at the time of presentation. Although platinum based chemotherapeutic regimens have recently emerged as the best option for producing a clinically significant response as reported in various case series, the response is far from satisfactory, as most RMC patients still succumb to their disease within a year of diagnosis. There is currently no standard of care for treatment of this disease. We report, to our knowledge, the first case of RMC where in molecular characterization of the tumor was used to guide therapy. In our patient, molecular analysis identified a decreased expression of Ribonucleotide Reductase M1(RRM1) and phosphatase and tensin homolog (PTEN). Based on these results of PTEN deficiency, we started our patient on everolimus (an MTOR inhibitor) maintenance after treating him with an induction chemotherapy regimen of Paclitaxel-Cisplatin-Gemcitabine (PCG). His tumor responded to induction therapy and he went into complete remission and remained in remission for 7 months. He is now alive about 14 months from his diagnosis and is asymptomatic with minimal disease. The rarity of RMC makes it very difficult to do any meaningful clinical trials in this group of patients. The overall prognosis for RMC remains very poor and knowledge about driver mutations may help in guiding therapy to improve survival in this select group of patients, where there is dearth of available therapies.

Introduction

Renal Medullary Carcinoma (RMC) is a rare tumor found predominantly in young patients with Sickle Cell Trait (SCT) or Sickle Cell Disease (SCD).[1,2] The disease is highly aggressive, typically presenting with widespread metastases at the time of diagnosis.[3] The disease is predominant in males (M:F = 2:1) with a median age of 26 years and the tumors commonly occur in the right kidney.[4] The pathogenesis of this disease is unknown but in some cases inactivation of SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) protein has been observed suggesting its role in the development of this disease.[4,5] Historically, patients would succumb to this disease within weeks to months with a median of <12 months.[1,6] Because of the rarity of the tumor and its vicious nature, clinical trials are difficult to perform. There are some case reports and case series[1] that hint toward the benefit of using cisplatin-based chemotherapy regimen in RMC but almost all of them relapsed quickly after treatment. The overall prognosis of this disease remains poor with no cure.

We present here what is, to our knowledge, the first case in which molecular analysis of the tumor was used to direct maintenance therapeutic approach post cisplatin-based chemotherapy in a patient with metastatic RMC.

Case Report

A 27 year-old African-American male with SCT presented with hematuria and left flank pain in June 2013. Computed tomography (CT) of the abdomen and pelvis revealed a poorly defined mass at the midpole of the left kidney, 4.8 × 4.4 cm in size, with minimal hydronephrosis (**Fig. 1**). CT guided biopsy of the mass was performed at an outside institution. The pathology

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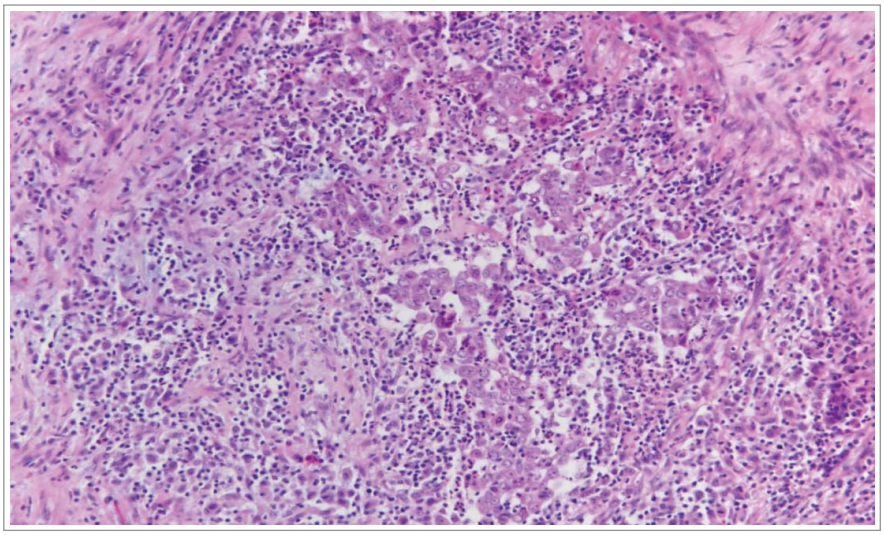

Figure 1. Pathological features of renal medullary carcinoma. Pathologic surgical specimen of left kidney, revealing highly atypical cells arranged in nests and sheets, with intratumoral neutrophilic infiltration and peritumoral inflammation and fibrosis.

came back as RMC. The patient underwent left radical nephrectomy without any complications in an outside institution. The surgical specimen contained highly atypical cells arranged in nests, sheets, and adenoid cystic patterns, with intratumoral neutrophilic infiltration and peritumoral inflammation and fibrosis (**Fig. 1**). Staining was positive for thrombomodulin, EMA, CAM5.2, PAX-8, high molecular weight keratin, and E-Cadherin; and negative for PAX-2, uroplakin, p63, and Mucicarmine. The tumor was 6.5 cm in its longest dimension, and was pathologically staged as pT3a pN1 Mx. He had not had a staging CT chest prior to his surgery. Five weeks post his surgery, in July 2013; he was referred to our institution for further management. At that time, he had noticed recurrence of his flank pain. CT of the chest, abdomen, and pelvis revealed mediastinal, hilar, and gastrohepatic ligament lymphadenopathy with right pulmonary nodules suspicious for metastatic disease (**Fig. 2**). Bone scan had shown suspicious lesion in the left 8th rib, which was thought to be a metastatic site. He was unable to start chemotherapy with cisplatin based regimen because of renal insufficiency and was instead started on carboplatin (AUC 6) and Paclitaxel (175 mg/m^2) Q3 weekly with denosumab (120 mg) Q6 weekly (per patients' request to decrease frequent hospital visits) with plans to switch to cisplatin based regimen when renal function improves.

We switched him to PCG (paclitaxel 80 mg/m2, cisplatin 35mg/m2 and gemcitabine 1000 mg/m2 on days 1 and 8 every 21 d), when his renal function stabilized with GFR >50. He tolerated the chemotherapy well except for myelosuppression needing dose reduction and addition of neulasta from his C#3 onwards. He got a total of 6 cycles with platinum based chemotherapy, out of which 5 were PCG. CT of chest and abdomen after cycle 2 of PCG revealed marked decrease mediastinal, hilar, and gastrohepatic ligament lymphadenopathy with complete resolution (CR) of lung nodules and lymph nodes post completion of cycle 4 of PCG chemotherapy (**Fig. 2**). Given the rarity of the tumor and no standard of care for treatment, his surgical specimen was sent to Caris Life Sciences for molecular profiling and next generation sequencing in the hopes of finding a targetable mutation. Tumor immunohistochemistry revealed below threshold expression of Ribonucleotide Reductase M1 (RRM1) expression (**Figs. 3A**), near complete loss of phosphatase and tensin homolog (PTEN) expression (Fig3 B) and 50% c-MET expression (positive but CISH was negative for cMET amplification); as shown in **Figure 4B**, loss of PTEN gene function removes the negative feedback mechanism exerted on PI3-kinanse, thereby increasing downstream signaling and increased un-inhibited cell growth. The tumor biomarker profile indicated potential benefit of gemcitabine, nab-paclitaxel, and doxorubicin. Since most of the literature showed that patients had early relapse of their disease post chemotherapy, we wanted to explore maintenance therapy for his disease to prevent early relapse.[1,7] His molecular analyses had shown low level of PTEN expression by IHC(5%), frequently correlated with PTEN gene deletion and functional loss. We opted to give him maintenance everolimus (mTOR-mammalian target of rapamycin, inhibitor) 10 mg/daily therapy, starting beginning of December 2013. **Figure 4C** demonstrates potential targets for therapy in patients with PTEN gene loss of function, including an MTOR inhibitor. His follow up bone scans were stable and upon repeat review, the rib lesion was thought to be a bony island of uncertain significance.

He tolerated everolimus well, follow up CT chest and abdomen showed maintenance of CR until the end of June 2014, when his imaging showed a significant increase in his mediastinal and hilar and aortocaval lymph nodes. However, all his nodes were less than 2 cm and he was clinically asymptomatic. The repeat biopsy from his aortocaval lymph node was positive for recurrence of his disease. He was switched to gemcitabine single agent therapy in July 2014 and continues to tolerate it well. He is presently alive and almost 14 months from his diagnosis. We had wanted a repeat biopsy for next generation sequencing but due to unavoidable circumstances this was not possible in spite of disease progression.

Discussion

The patient in this study presented with RMC that was widely metastatic shortly after the time of presentation. We had done molecular profiling to determine possible targets with intent to treat. He was found to have near absence of PTEN expression by immunohistochemistry and we used this information to guide

his maintenance therapy (**Fig.** 4C). He tolerated this therapy well with no significant side-effect and was in clinical and radiological remission for 7 months since stopping of his induction chemotherapy and is now alive about 14 months since his diagnosis. Our case is one of the very few cases with advanced RMC who achieved CR from his initial chemotherapy. To the best of our knowledge, this is the first case to show that profiling and subsequent targeted therapy had therapeutic benefit in RMC and should be considered in these patients. Our patient is alive; about 14 months post his diagnosis.

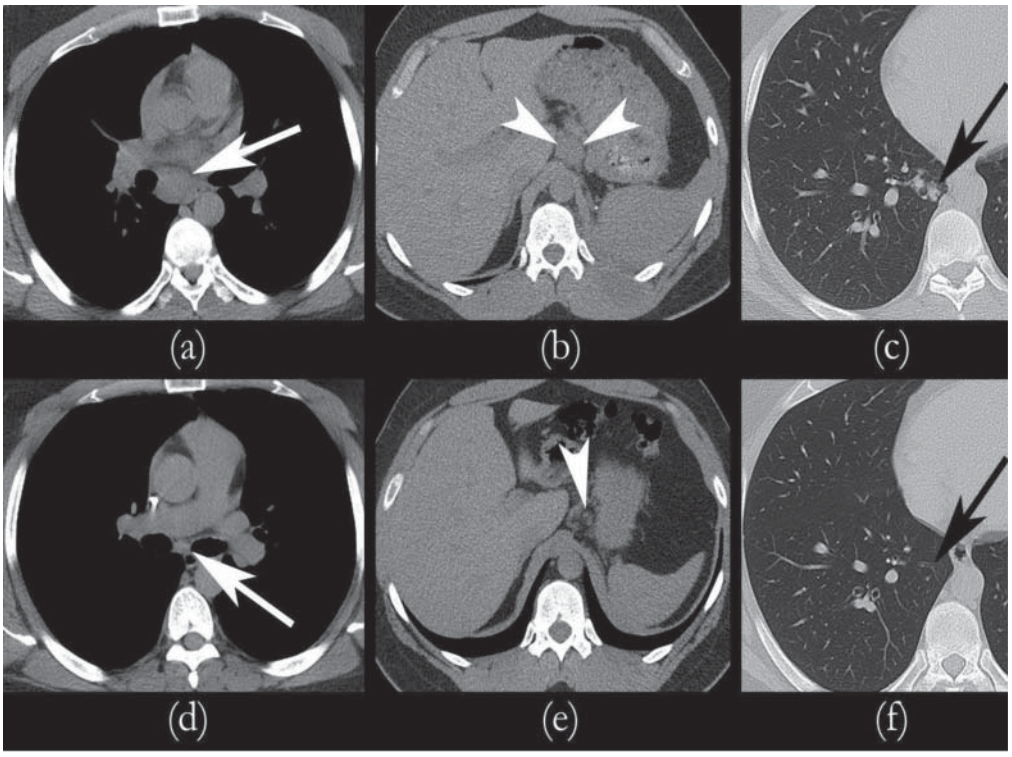

Figure 2. Sequential CT scans showing response to therapy. Metastatic Renal Medullary Carcinoma with Complete Remission of Disease post chemotherapy and it remained the same while on maintenance: CT scan prior to the initiation of chemotherapy revealed significant lymphadenopathy consistent with metastatic disease in the mediastinum (**A**), gastrohepatic ligament (**B**), and in the right lung (**C**). After Cycle 4 of chemotherapy, CT imaging revealed complete remission of mediastinal (**D**), gastrohepatic ligament (**E**), and pulmonary (**F**) nodules.

RMC was first described in 1995 by Davis et al as "the seventh sickle cell nephropathy." Since that initial publication, the literature has become populated with case reports and periodic reviews of the literature, which form the principle body of knowledge available on this tumor. The disease is usually widely metastatic at the time of diagnosis. The tumor microscopically presents with islands of reticular growth, with adenoid cystic-like spaces, solid sheets, and anastomosing tubules.[8] The cancer cells are highly atypical, with a rhabdoid or plasmacytoid shape as well as dark cytoplasm, clear nuclei, and prominent nucleoli.[9] Prominent fibrosis and inflammation are characteristic.

Historically, the prognosis of this tumor has been dismal, with patients surviving approximately weeks to months. We searched for all English-language case reports for adult patients (>18 y of age; we have included one case of 17 y old who had an amplification of ABL-tyrosine kinase) with RMC that was metastatic at or shortly after the time of diagnosis, published since 2003, and gathered available data on these cases pertaining to chemotherapy protocols and survival since the time of the diagnosis (**Table 1**). We only included patients from the case reports or case series who had data for chemotherapy use, survival post diagnosis and or response to therapy. Our search returned 34 unique cases published during that time, out of which only 17 cases met

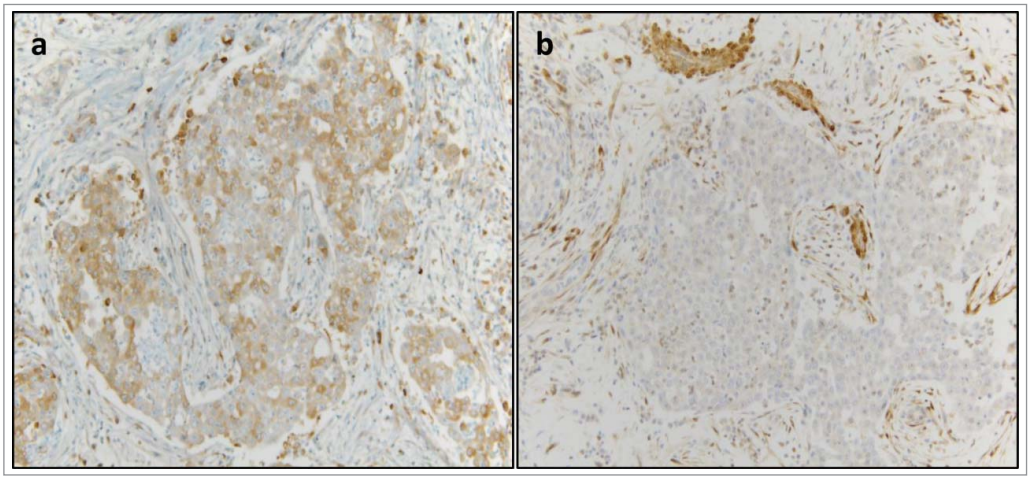

Figure 3. Immunohistochemical Identification of Molecular Targets for Therapy. (**A**) Negative expression of RRM1 (defined as less than 2+/50%) was detected in the patient sample (1+/90%). (**B**) Negative expression of PTEN (defined as ≤1+/50%) was detected in the patient sample (1+/5%, a near complete loss of expression).

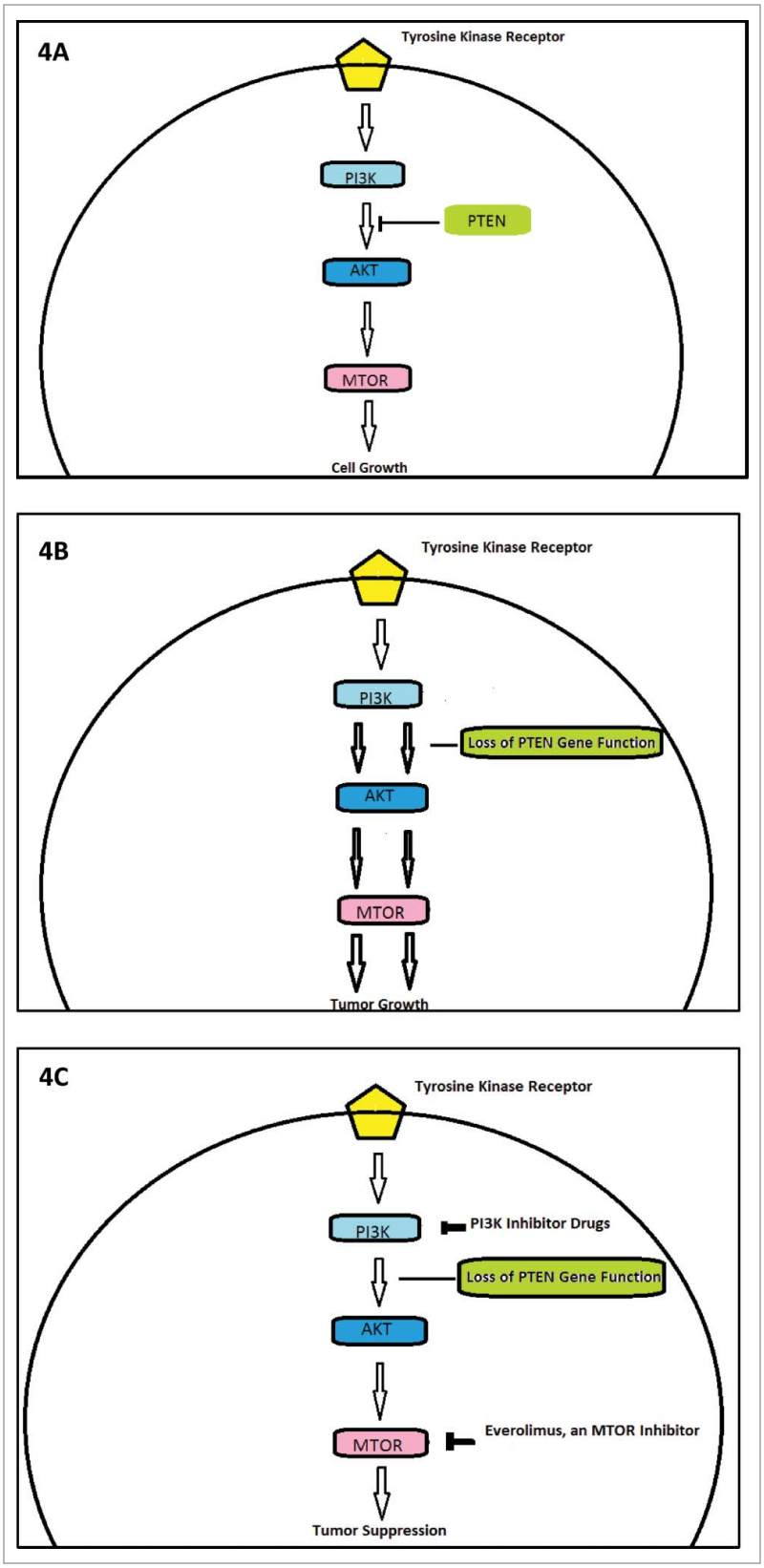

Figure 4. Outline of the role of PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; mTOR, mammalian target of rapamycin. (**A**) Exhibits role of tumor suppressor gene PTEN in regulating PI3K mediated cell cycle signaling. (**B**) Demonstrates role of loss of PTEN inhibition in tumor genesis. (**C**) Highlights potential targets of cell cycle inhibitor, including Everolimus which was used in our patient.

our above mentioned criteria for inclusion in the **Table 1**.[1,10-17] The median survival calculated for all included patients in the **Table 1** was 10.75 months with an average of 10.9 months. We observed that the majority of patients who had any meaningful response (complete or partial response) were treated with cisplatin based chemotherapy (survival appeared to be more extended with PCG regimen when compared to the rest). Majority of these patients had right sided kidney RMC. The observation of positive response to cisplatin appears to be consistent with the previously published notion that renal medullary carcinoma may respond to platinum-based agents.[18,10] While these regimens have improved survival compared to the original studies, they still universally fail to produce a durable response or cure.

The difficulty in achieving durable responses for this tumor may reflect our poor understanding of its pathophysiology. A report by Swartz et al.[19] has shown a strong expression of Vascular Endothelial Growth Factor (VEGF), and Hypoxia Inducible Factor (HIF) in RMC.[19] These findings formed the basis for a pathophysiologic theory, which proposes that the low oxygen tension in the renal medulla, especially in patients with sickle cell hemoglobinopathies, promotes the expression of HIF. Under normal circumstances, HIF leads to upregulation of p53, ultimately causing apoptosis. In the setting of deficient or absent p53, however, HIF instead leads to VEGF expression, which may help tumor vascularization and growth. In a separate report, Yang et al. suggested presence of hypoxia related and unrelated genetic abnormalities in significant number of cases, and hinted their role in the pathogenesis of RMC.[20] Recent studies looking into the cytogenetic abnormalities of RMC have failed to identify any consistent abnormalities across cases, and have also brought into question the aforementioned theory by Swartz on the grounds of cases in caucasian patients without hemoglobinopathies.[21,22] Gao et al., had recently shown involvement of genes in signaling pathways such as phosphatidylinositol 3-kinasePIK3C2G), cell cycle control (CDC25D and CDC73), and histone synthesis (HIST2H3D) based on molecular analysis of 11 patient specimens in a retrospective fashion. Although mechanism of pathogenesis still remains largely elusive, these alterations may become probable targets for therapy in the future.[23]

It is both the lack of complete understanding of the disease and rarity of desirable response to treatment that led us to our treatment approach. The fact that RMC is probably sensitive to

Table 1. Relevant cases with renal medullary carcinomas and their survival

Reference	Age	Surgical Treatment	Chemotherapy Regimen	Response	Survival from Diagnosis (weeks)
1	23	None	Sutent f/u GC	PD	2
1	24	RN	PCG	PR	32
1	24	RN	GC	PR	20
1	30	RN	GC f/u by doxorubicin f/u by sutent	NA	104
1	24	None	GCa	SD	24
11	20	None – unresectable	PCG	PR	42
18	51	Nephrectomy	PCa f/u everolimus**	PR for 4 months after 6 cycles f/u PD	60
18	32	Nephrectomy +partial ureterectomy	Sunitinib (4 wk on clinical trial)/ PCa	SD after 2 cycles of PCa f/u PD after 4 cycles	44
12	17***	Nephrectomy	Imatinib (4wks)/ MVAC	PD on imatinib f/u by PR post MVAC	52
12	30	None	MVAC	PR f/u by decline and he only got 2 cycles of MVAC	14
12	48	Nephrectomy+ ureterectomy	Sunitinib (4wks)/ MVAC	PR	68
16	33	None	MVAC	SD on initial scan f/u PD	28
17	35	Nephrectomy	PCG (6 mo)/ Salvage: AG	CR*	108
13	25	Nephrectomy	MVAC	NA	16
20	19	None	GC	NA	24
14	34	Not specified	GCa	PR	52
15	19	Nephrectomy after 3x MVAC	MVAC f/u GD f/u ICE f/u TC	PR	52

Abbreviations: RN-radical nephrectomy; GC-gemcitabine and cisplatin; GCa- gemcitabine and carboplatin; PCG- paclitaxel, cisplatin, gemcitabine: PCaG-paclitaxel, carboplatin, gemcitabine; PCa-carboplatin, paclitaxel; MVAC-methotrexate, vinblastine, doxorubicin, cisplatin; AG-adriamycin, gemcitabine; EDCV-Etoposide, Doxorubicin, Cyclophospamide, Vincristine; GD- gemcitabine, docetaxel; ICE- ifosfamide, carboplatin, etoposide; TC-thalidomide, capecitabine; PD-progressive disease; PR- partial response; SD-stable disease; NA-not available; f/u ,followed by *-post salvage. He had topoII increased expression by immunohistochemistry; **- no response to everolimus and it was used as last resort for a few weeks. Reason to start this unclear but she died very shortly after that; ***- this is the only patient we have included who is <18 years because her tumor had amplification of ABL-tyrosine kinase.

platinum based chemotherapy, coupled with the low expression/absence of RRM1 in his tumor; may have contributed to the complete remission of our patient's disease when treated with PCG chemotherapy regimen. Whether the low RRM1 expression facilitated a strong response to gemcitabine component in PCG is difficult to determine. The decision to attempt the use of everolimus for maintenance therapy, however, was entirely guided and deemed feasible based on the information regarding loss of PTEN expression gained from IHC profiling of the tumor. It is well known that PTEN deletion causes upregulation of PI3K-AKT pathway which plays a significant role in proliferation and progression of cancer and since mTOR is a downstream signal for the PI3K-AKT pathway, blocking this mTOR signal may cause decrease in tumor proliferation.[24] There is literature supporting PTEN deletion being a marker for predicting response to everolimus in other cancer types such as prostate cancer and that was our rationale for using everolimus in this patient.[24]

Conclusion

We acknowledge that molecular profiling with next generation sequencing is not feasible, nor is it necessary for every patient with a malignant tumor. However, for these rare tumor types, especially those in which treatment guidelines are not well established, comprehensive molecular characterization may provide an invaluable insight for choosing a more personalized therapeutic approach. The information from molecular profiling can be used to guide maintenance therapy with targeted agents, which are better tolerated than chemotherapy and may provide a road to prolonged survival in patients with this deadly disease in this current era of personalized medicine.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Ethical Statement

The authors complied with patient confidentiality. An informed consent was obtained by the patient prior to preparing this manuscript.

Authors Contribution

JSL and SMR- manuscript preparation and both contributed equally to be co-first authors; ZG and NES- manuscript preparation, critical review of the article; SLH, MK and JJD provided critical review of the article; MJ-manuscript preparation, critical review/revision of the article and patient care.

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