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Prolonged Remission of Upper Urinary Tract Urothelial carcinoma with Prominent Choriocarcinomatous Differentiation: A Case Report

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Keywords

choriocarcinoma; renal pelvis; upper urinary tract

Introduction

Although >95% of testicular germ cell tumors are curable when appropriately treated, pure testicular choriocarcinoma carries a poor prognosis with a 5-year survival of <80% in the USA.¹ This testicular cancer variant often presents with high levels of serum beta human chorionic gonadotropin (β -hCG) levels and widespread metastases with rapid disease progression.² To achieve a cure, β -hCG levels must become undetectable. Persisting β -hCG levels, even after clinical evidence of disease resolution, reflect residual tumor and eventual relapse.^{2, 3}

Primary male choriocarcinoma of the upper urinary tract is an extremely rare malignancy with fewer than 10 cases reported in the literature.^{4–11} Many of these tumors are thought to arise from trophoblastic (choriocarcinomatous) differentiation of high-grade urothelial carcinoma.^{4, 7–10} Herein, we describe a male patient with choriocarcinoma of the renal pelvis, likely of urothelial origin, who was successfully treated with nephrectomy followed by multiple sequential chemotherapy regimens.

Case report

A 48-year-old Hispanic gentleman developed left-sided flank pain and gross hematuria in the summer of 2013. The patient had never smoked, occasionally drank alcohol, and did not abuse recreational drugs. He had served in the military from 1984 to 1994 and at the time of presentation worked in information technology (IT) support. His family history included a maternal grandfather with gastric cancer and an aunt with breast cancer. On examination, he

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had normal chest, lung, abdominal, and scrotal examinations. CT imaging revealed a left kidney mass, as well as multiple bilateral lung nodules consistent with metastatic disease. On 07/08/2013, the patient underwent left nephroureterectomy. Pathology revealed a choriocarcinoma, 9.5 cm in greatest dimension. The multinucleated syncytiotrophoblasts (Figure) demonstrated positive immunohistochemical staining for β -hCG, SALL-4, GATA 3, Pin dual and inhibin, as well as negative staining for cytokeratin 20, RCC, PAX-8, p63, OCT-3/4, thrombomodulin and Glypican-3. The mononuclear cytotrophoblasts stained positive for cytokeratin 7 and cytokeratin AE1/AE3. Fluorescence in situ hybridization (FISH) testing for isochromosome 12p was negative. Although 82% of cells had additional copies of chromosome 12, this was deemed to be a nonspecific result that is also found in tumors of non-germ cell origin.^{10, 12} Immunoreactivity for GATA 3 provided evidence towards a urothelial origin of the tumor. Accordingly, the tumor was deemed to represent a urothelial carcinoma with prominent choriocarcinomatous differentiation. This was further supported by the presence on bladder biopsy of a high grade non-invasive papillary urothelial carcinoma (stage Ta). Molecular analysis of a 50-gene panel using a Clinical Laboratory Improvement Amendments (CLIA) - certified next generation sequencing platform (Table 1) revealed only a single mutation in the codon 271, exon 8 (GAG to AAG) of the TP53 gene that changed the encoded amino acid from Glutamate to Lysine (c. 811G>A p.E271K). This mutation was present at a low (< 10%) allelic frequency. A relatively common germline polymorphism was also noted in codon 541, exon 10 (ATG to CTG) of the KIT gene that would change the encoded amino acid from Methionine to Leucine (c.1621A>C p.M541L).

Subsequent scrotal ultrasound on 7/19/13 was negative for any testicular mass. At the same time, our patient's post-nephrectomy serum β -hCG was 5277 milli-international units per milliliter (mIU/mL) and his alpha-fetoprotein (AFP) levels were 1.7 nanogram/milliliter (ng/mL). His lactate dehydrogenase (LDH) was not elevated. Ten days later, his β -hCG had more than doubled to 11474 mIU/mL. His creatinine levels were 1.63 mg/dL with an estimated glomerular filtration rate (eGFR) of 45 mL/min/1.73m² by the Modification of Diet in Renal Disease (MDRD) method. MRI of the brain with and without intravenous contrast on 7/31/13 was negative for intracranial metastases. Given the aggressiveness of the tumor, we decided to quickly initiate chemotherapy using a regimen with relatively low risk for nephrotoxicity and thrombocytopenia/bleeding that would be active against both choriocarcinoma and urothelial carcinoma. We accordingly initiated weekly intravenous (IV) adriamycin 30 mg/m², paclitaxel 100 mg/m², and cisplatin 30 mg/m² (ATP regimen) on 7/31/13 with brisk IV fluid hydration. The patient's β -hCG on 8/6/13 increased to 17171 mIU/mL presumably due to tumor cell death. Indeed, at the time of dose#3 of ATP on 8/13/13, his β -hCG had decreased to 6601.8 mIU/mL. Due to progressive decline in absolute neutrophil count, this cycle was given with pegfilgrastim support. The patient also developed shingles at the T10 dermatome for which he was started on a 7-day course of valacyclovir 1 gr every 12 hours followed by 500 mg daily.

By 8/27/13 the patient's creatinine had steadily increased to 1.77 md/dL. Subsequently, his regimen was switched on that day to IV gemcitabine 900 mg/m², paclitaxel 135 mg/m², and adriamycin 30 mg/m² (GTA) with pegfilgrastim support. By that time, his β -hCG had declined to 126.5 mIU/mL. Cycle # 2 of GTA was given on 9/12/13, at which point the

patient's serum β -hCG was 18.5 mIU/mL. However, on the day of the 3rd GTA cycle (9/26/14) β -hCG persisted at 7.3 mIU/mL. To rule out hypogonadism we administered a dose of Testosterone Cypionate 200 mg intramuscularly. Unfortunately, β -hCG persisted at 3.4 mIU/mL on 10/10/13. Given this ominous finding, and his relatively stable kidney function, we switched to a standard testicular cancer (BEP) regimen of bleomycin 30 units/day on days 1, 8, and 15, etoposide 100 mg/m²/day on days 1–5, and cisplatin 20 mg/m²/day on days 1–5 with brisk IV fluid hydration as an inpatient and no pegfilgrastim support. The patient received 1 cycle of BEP on 10/10/13 with a decline of β -hCG to 1.3 mIU/mL by 11/4/13. However, he developed severe peripheral neuropathy that precluded further administration of this regimen. We therefore again decided to switch therapy to actinomycin D, cyclophosphamide and etoposide followed by cisplatin, vincristine, methotrexate, bleomycin (POMB/ACE) given a prior report of efficacy with this regimen in male upper urinary tract choriocarcinoma.⁶ Accordingly, on 11/04/13 the patient was started on actinomycin D 0.5 mg daily on days 3–5, cyclophosphamide 500 mg/m² IV on day 5, and etoposide 100 mg/m² on days 1–5 (ACE), with pegfilgrastim support. He also received another dose of testosterone supplementation to minimize any chance of spurious β -hCG readings.

After receiving 1 dose of ACE, the patient's β -hCG became undetectable by 11/25/13. CT imaging, however, showed interval increase in the number and sizes of the pulmonary nodules, concerning for progressive pulmonary metastases when compared with prior imaging studies (7/2/13). We decided not to proceed with POMP and instead biopsy the lung nodules on 12/13/13 to determine if there was any remaining urothelial or teratomatous component. The biopsy revealed extensive necrosis without any viable tumor present. The patient was subsequently followed closely with CT imaging and serum markers every 3 months. His β -hCG has remained negative since that time. His lung nodules also remained relatively stable, although 6 lesions on the left lung demonstrated a mild, but concerning, increase in size over time. Therefore, on 6/8/15, left thoracotomy with wedge resection of these 6 nodules along with mediastinal dissection of a level 9L lymph node was performed. No viable tumor was present in any of the resected tissues. A cystoscopy on 1/13/2016 was negative for any tumor. The patient has recovered from his peripheral neuropathy and has remained disease-free to this day.

Discussion

Based on the small number of case reports available in the literature, the majority of primary choriocarcinomas of the upper urinary tract appear to have originated from trophoblastic differentiation of urothelial cells.^{4, 7–10} One study found that 9 out of 47 high-grade urothelial neoplasms expressed hCG on immunohistochemistry, and two of these tumors demonstrated trophoblastic-like differentiation.⁹ Alternatively, choriocarcinomas may originate from multipotent embryonal cells that became arrested during migration in ectopic locations. However, the majority of such extragonadal germ cell tumors arise from midline structures anywhere between the level of the pineal gland to the coccyx.^{13, 14} Extragonadal choriocarcinomas may also be metastases from a primary testicular origin that has spontaneously regressed. However, renal metastasis of testicular choriocarcinomas is extremely rare.

In the present case, the absence of isochromosome 12p (a specific marker of germ cell tumors¹⁵), positive immunoreactivity for GATA 3 (a relatively specific marker for urothelial carcinoma¹⁶), and presence of a concurrent stage Ta high grade non-invasive papillary urothelial carcinoma of the bladder (suggestive of field cancerization or seeding of cancer cells¹⁷) all point towards a diagnosis of urothelial carcinoma with choriocarcinomatous differentiation. Ideally, such tumors should be treated with chemotherapy prior to nephroureterectomy, similarly to other high-grade upper tract urothelial malignancies¹⁸ and to choriocarcinoma in women.¹⁹ However, because these tumors clinically mimic the more common renal cell carcinoma, preoperative β -hCG levels will most often not be available, the diagnosis will be established following nephroureterectomy, and chemotherapy will be given post-surgery.

Conclusion

The present case posed a therapeutic dilemma due to our patient's compromised renal function after his nephroureterectomy. Given the aggressiveness and likely urothelial origin of choriocarcinomas of the upper urinary tract, nephron-sparing regimens, such as ATP and GTA, that are active against both choriocarcinoma and urothelial carcinoma can be effectively used. Given the high risk of relapse of choriocarcinomas with persisting serum β -hCG, this marker must become undetectable to ensure a cure. We were able to achieve this effect, and thus produce a prolonged remission, by consolidation with BEP followed by ACE.

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Clinical Practice Points

- The clinical presentation of male choriocarcinomas of the upper urinary tract is often similar to renal cell carcinoma and may include flank pain, macrohematuria, and a large kidney mass with pulmonary metastases.
- Diagnosis is frequently established after nephroureterectomy, which may complicate cisplatin-based chemotherapy regimens.
- To achieve a cure, serum β -hCG levels must become undetectable.
- Herein we describe the first case of a male patient with a choriocarcinomatous tumor of the renal pelvis and metastases to the lungs who has achieved complete remission for almost 3 years to date following sequential adriamycin, paclitaxel, and cisplatin (ATP) $\times$ 3 doses, gemcitabine, paclitaxel, and adriamycin (GTA) $\times$ 3 doses, standard bleomycin, etoposide, and cisplatin (BEP) $\times$ 1 dose, and actinomycin-D, cyclophosphade, and etoposide (ACE) $\times$ 1 dose.

Figure.

A) H&E sections show a poorly differentiated carcinoma with hemorrhage and alternating arrangement of mononucleated trophoblastic cells (arrow head) and syncytiotrophoblastic cells (arrow); B) Higher power high mitotic rate and cytological atypia; C) Tumor cells are positive for HCG; D) Tumor cells are positive for GATA-3.

Table 1

Mutation analysis of the patient's tumor using a 50-gene next generation sequencing platform

Gene	Exons (codons) tested	Result
ABL1	4 (232–260), 5 (275–279), 6 (314–360), 7 (380–412)	No mutation detected
AKT1	3 (16–52), 6 (154–183)	No mutation detected
ALK	23 (1172–1204), 25 (1270–1279)	No mutation detected
APC	16 (860–891), 16 (1089–1125), 16 (1284–1326), 16 (1342–1384), 16 (1426–1471), 16 (1483–1524), 16 (1543–1582)	No mutation detected
ATM	8 (326–355), 9 (407–412), 12 (601–626), 17 (834–865), 26 (1292–1325), 34 (1674–1707), 35 (1726–1757), 36 (1790–1815), 39 (1926–1946), 50 (2436–2454), 54 (2650–2667), 55 (2682–2711), 56 (2718–2736), 59 (2865–2891), 61 (2933–2950), 63 (2996–3026), 63 (3041–3057)	No mutation detected
BRAF	11 (439–473), 15 (581–611)	No mutation detected
CDH1	3 (65–96), 8 (337–374), 9 (380–408)	No mutation detected
CDKN2A	2 (51–90), 2 (98–140)	No mutation detected
CSF1R	7 (297–319), 22 (953–973)	No mutation detected
CTNNB1	3 (9–48)	No mutation detected
EGFR	3 (96–123), 7 (279–297), 15 (575–601), 18 (695–726), 19 (729–761), 20 (762–796), 20 (807–823), 21 (855–875)	No mutation detected
ERBB2	19 (752–769), 20 (770–797), 21 (839–882)	No mutation detected
ERBB4	3 (136–141), 4 (167–186), 6 (225–247), 7 (254–290), 8 (295–323), 9 (333–367), 15 (580–623), 23 (919–948)	No mutation detected
EZH2	16 (625–649)	No mutation detected
FBXW7	5 (264–287), 8 (378–403), 9 (434–473), 10 (478–509), 11 (567–594)	No mutation detected
FGFR1	4 (120–148), 7 (247–273)	No mutation detected
FGFR2	7 (250–275), 7 (296–313), 9 (362–399), 12 (546–558)	No mutation detected
FGFR3	7 (247–277), 9 (367–402), 14 (631–653), 16 (690–719), 18 (771–807)	No mutation detected
FLT3	11 (437–466), 14 (570–610), 16 (663–685), 20 (828–847)	No mutation detected
GNAI1	5 (202–219)	No mutation detected
GNAQ	5 (206–245)	No mutation detected
GNAS	8 (196–220), 9 (220–240)	No mutation detected
HNF1A	3 (192–221), 4 (253–282)	No mutation detected
HRAS	2 (5–35), 3 (42–82)	No mutation detected
IDH1	4 (101–135)	No mutation detected
IDH2	4 (133–177)	No mutation detected
JAK2	14 (603–622)	No mutation detected
JAK3	4 (128–140), 13 (568–580), 16 (709–733)	No mutation detected
KDR	6 (244–266), 7 (267–291), 11 (471–480), 19 (872–894), 21 (961–988), 26 (1135–1156), 27 (1192–1221), 30 (1283–1310), 30 (1324–1357)	No mutation detected
KIT	2 (23–58), 9 (494–514), 10 (525–549), 11 (550–587), 13 (627–661), 14 (664–684), 15 (714–724), 17 (802–828), 18 (832–858)	Variant detected in codon 541, exon 10 (ATG to CTG): c.1621A>C p.M541L. Probable germline polymorphism.
KRAS	2 (5–37), 3 (38–66), 4 (114–150)	No mutation detected
MET	2 (159–188), 2 (339–378), 11 (816–856), 14 (981–1012), 16 (1105–1132), 19 (1246–1274)	No mutation detected
MLH1	12 (373–415)	No mutation detected

Gene	Exons (codons) tested	Result
MPL	10 (501–522)	No mutation detected
NOTCH1	26 (1566–1602), 27 (1673–1680), 34 (2436–2476)	No mutation detected
NPM1	11 (283–295)	No mutation detected
NRAS	2 (3–31), 3 (43–69), 4 (124–150)	No mutation detected
PDGFRA	12 (552–583), 14 (644–668), 15 (671–709), 18 (819–854)	No mutation detected
PIK3CA	2 (54–90), 2 (106–118), 5 (316–351), 7 (390–417), 8 (418–422), 8 (449–468), 10 (522–549), 14 (677–720), 19 (898–924), 21 (1017–1051), 21 (1065–1069)	No mutation detected
PTEN	1 (1–25), 3 (55–70), 5 (99–135), 6 (165–184), 7 (212–215), 7 (231–267), 8 (282–300), 8 (312–342)	No mutation detected
PTPN11	3 (46–82), 13 (485–527)	No mutation detected
RB1	4 (130–159), 6 (196–203), 10 (314–345), 11 (350–366), 14 (452–463), 17 (547–565), 18 (566–582), 20 (655–691), 21 (703–724), 22 (743–770)	No mutation detected
RET	10 (608–627), 11 (627–654), 13 (762–786), 15 (875–910), 16 (911–924)	No mutation detected
SMAD4	3 (98–136), 4 (142–146), 5 (165–202), 6 (242–263), 8 (307–319), 9 (326–365), 10 (384–424), 11 (443–474), 12 (494–532)	No mutation detected
SMARCB1	2 (35–72), 4 (144–167), 5 (167–206), 9 (373–386)	No mutation detected
SMP	3 (186–228), 5 (307–331), 6 (391–419), 9 (511–542), 11 (608–646)	No mutation detected
SRC	14 (499–533)	No mutation detected
STK11	1 (22–64), 4 (155–181), 4 (191–199), 5 (200–207), 6 (253–285), 8 (317–361)	No mutation detected
TP53	2 (1–20), 4 (68–113), 5 (126–138), 5 (149–187), 6 (187–223), 7 (225–258), 8 (263–307), 10 (332–367)	Mutation detected in codon 271, exon 8 (GAG to AAG): c.811G>A p.E271K
VHL	1 (78–108), 2 (114–150), 3 (155–174)	No mutation detected