Case Report

A unique case of transitional cell carcinoma of renal pelvis in a patient with Lynch syndrome

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Abstract

Lynch syndrome-associated transitional cell carcinoma of the upper urinary tract is uncommon. Lynch syndrome is a well-known inherited condition with particularly increased risk of colorectal cancers and a lesser extent other types of cancers. We present a rare case of urothelial cancer associated with Lynch syndrome from the time of its diagnosis to its multidisciplinary management to date. This case report outlines the unique characteristics of the case. The patient was positive for a mutation in the MLH1 gene, a known mutation of Lynch syndrome, which has a sparse association to Lynch syndrome-related urothelial carcinoma compared to other genes, e.g., MSH2. The patient's second-degree relative had confirmed Lynch syndrome with the same MLH1 genetic mutation and had colorectal cancer. The first-degree female relative of the patient with urothelial cancer had breast cancer, also not commonly associated with Lynch syndrome. The patient's age at the time of diagnosis of urothelial cancer was 46 years, which is at the lower end of the spectrum of the average age of Lynch syndrome associated with urothelial cancers. This paper also presents a review of the literature regarding upper urinary tract transitional cell carcinoma, its association with Lynch syndrome and various opinions on screening guidelines for urothelial cancer in relatives of a patient diagnosed with Lynch syndrome.

Keywords: hereditary nonpolyposis colorectal cancer, Lynch syndrome, renal pelvis, transitional cell carcinoma, urinary tract

Introduction

The mucosal surface layer of renal collecting tubules, calyces and pelvis, ureter, bladder and down to urethra are made of similar type of epithelial cells called urothelium [1]. Urothelial cancer, also known as transitional cell carcinoma, is the fourth most common cancer occurring in the United States and it is estimated to be the cause of 4-5% male cancer-related deaths [2]. Majority of cases of urothelial cancer (UC) are in the urinary bladder [1]. Upper urinary tract transitional cell carcinoma (UUTC) is localized to the renal pelvicalyceal system with potential ureter involvement and account for 5-10% of all urothelial cancers [1-3]. UUTC in general population is more common in men than in women, with a male-to-female ratio of 2:1 [1].

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There are environmental and genetic risk factors for UUTC. Environmental or acquired causes of UUTC include smoking, exposure to aromatic amines, phenacetine, Balkan endemic nephropathy and Chinese herb nephropathy [1]. The less common causes of UUTC are genetic factors like Hereditary Nonpolyposis Colorectal Cancer (HNPCC), also known as Lynch syndrome [1,2]. Lynch syndrome (LS) is an autosomal dominant inherited condition in a small number of genes with increased risk for colorectal and endometrial cancers [1,2,4]. UUTC occur in 5% of patients with LS, making it the third most common malignancy in patients with LS [2]. LS is associated with 20 times more risk of UC than normal population [5]. Surgical resection plays a crucial role in the treatment of UC and extent of resection depends on the stage or grade of the disease [3,6]. For in-situ and localized tumors, chemotherapeutic agents typically used include BCG, mitomycin-C, thiotepa or adriamycin [3]. For advanced metastatic disease or with positive margins post-surgery or with lymph nodes involvement, cisplatin-based chemotherapy remains the standard of care [3]. The use of adjuvant radiotherapy for the treatment of advanced metastatic UC is nonconclusive [3,6]. There are different opinions to promulgate standardized screening guidelines for UUTC associated with LS, similar to the established screening guidelines for colorectal cancers associated with LS. One school of thought recommends in favor of these guidelines, given the high risk of UUTC with LS [5]. On the contrary, due to high false-positive rates and low sensitivity of the screening tests, there is opinion for careful review of patient cases before formulating screening guidelines [7].

Case
A 46-year-old Hispanic male presented with gross hematuria. Computed tomography (CT) of the abdomen and pelvis revealed a 2.1x2.4x1.2 cm infiltrating mass in the left kidney arising from the lower pole infundibulum extending into the lower pole calyces of the left kidney, consistent with infiltrating mass of the collecting system (Figure 1). The proximal left ureter was normal with no additional implants or findings. No drop metastases into the left ureter or contained within the bladder were noted. The periaortic and pericaval spaces were normal with no evidence of retroperitoneal lymphadenopathy.

Cystoscopy revealed a filling defect within the left lower pole and renal pelvis. He underwent ureteroscopy with biopsy and pathology report revealed high-grade urothelial carcinoma (Figure 2). On initial diagnosis, there was no evidence of transitional cell carcinoma of the bladder or the right kidney and no evidence of metastases. He underwent laparoscopic left nephroureterectomy. Post-surgery pathology report confirmed high-grade urothelial carcinoma, fragmented with blood clots and necrotic tissue. The tumor invaded beyond the muscularis propria into the renal parenchyma. Findings were suspicious of lymphovascular invasion and based on pathology specimen the tumor was staged as T3Nx (Figure 3).

Two months after surgery, the cystoscopy revealed non-invasive papillary urothelial carcinoma in the bladder which was treated with mitomycin-C. CT scan of chest and abdomen, about three months after surgery, showed a 9 mm right lower lobe nodule, left-sided enlarged supraclavicular lymph node and enlarged retroperitoneal nodes, worrisome for metastatic disease (Figure 4). CT guided biopsy of suspicious left supraclavicular lymph node came back diagnosis for metastatic papillary urothelial carcinoma. In view of chronic kidney disease (CKD) with GFR around 50s and considering nephrotoxic side effects of cisplatin, he did not receive cisplatin-based chemotherapy for his metastatic UC. Alternatively, for his metastatic UC, he was started on immunotherapy with pembrolizumab (anti-PD1 inhibitor) every three weeks.
Figure 2. After left nephroureterectomy, high power view of transitional cell (urothelial) carcinoma from a section of the left renal pelvis.

Figure 3. Lymphovascular invasion of transitional cell (urothelial) carcinoma into a renal vessel.

Figure 4. After left nephroureterectomy, axial contrast-enhanced CT of the abdomen performed four months later after the first CT as shown in Figure 1. Enlarging retroperitoneal lymph nodes (orange arrowheads) are consistent with nodal metastases. The left kidney is now absent.
As a follow-up to monitor disease progression and treatment response, the patient obtained CT of the thoracoabdominal region about every three months. Repeat CT scans at seven months revealed stable right lower 9 mm lung node and no progressive enlargement of supraclavicular, axillary, hilar or intra-abdominal lymph nodes. Before nephroureterectomy, the patient had CKD3a with GFR in 50s. Post-surgery, for 2 years, the patient's renal function remained stable in CKD3b range with GFR in 40s.

Our patient with UUTC had a first-degree female relative who had a history of breast cancer. The patient's second-degree male relative had a confirmed case of right-sided colorectal cancer. The second-degree relative had his entire right colon, including terminal ileum and appendix, resected. Pathology confirmed T3N1aM0, invasive moderately differentiated adenocarcinoma, metastatic to one lymph node. The patient (diagnosed with UUTC) and his second-degree relative (diagnosed with colorectal cancer), both tested positive for heterozygous c.208.1G>A genetic mutation in the MLH1 gene, consistent with LS.

Due to the diagnosis of LS mutation in multiple family members, genetic counseling on LS spectrum of cancers including colorectal, endometrial and urothelial cancers was recommended to the patient and his relatives. Presently, he is at over 20 months post-surgery and does not have clinical or radiologic evidence of worsening disease progression. He is doing well and able to perform his professional duties related to public service with good functional status.

**Discussion**

In the general population, renal cell carcinoma accounts for 90% of UUTC, whereas urothelial tumors account for only about 5% [5]. Majority of cases of UC are in the urinary bladder [1]. UUTC is localized to the renal pelvicalyceal system and/or ureter and accounts for 5-10% of all urothelial tumors with most lesions are found in renal pelvis [1-3].

There are genetic and environmental factors for urothelial cancers [1]. We restrict our discussion to genetic causes of UUTC associated with LS. LS is an autosomal dominant inherited condition due to mutations in genes that are responsible for repairing DNA replication errors, known as mismatch repair (MMR) genes [4,5]. Mutation defects in MMR genes cause replication errors in highly repetitive regions of DNA, called microsatellites, resulting in microsatellite instability (MSI). Uncorrected replication errors in areas of DNA responsible for controlling cell growth and apoptosis can lead to tumor growth [5,8]. For instance, MLH1 mutation, a gene associated with LS, is found to have an adverse impact on the apoptotic potential of cancer cells [9]. Presently, the set of LS associated genes includes MSH2, MLH1, MSH6, PMS1 and PMS2 [4]. Mutation carriers in MMR genes are not only at risk for developing cancers primarily in the colon, rectum and endometrium, but also other extracolonic cancers of the small bowel, stomach, hepatobiliary tract, skin and brain and cancers of the genitourinary tract [4,5,7,8]. In fact, upper urinary tract tumors, e.g., ureter and renal pelvis, are a part of "classical" spectrum of HNPPC tumors [10]. Additionally, the "atypical" spectrum of HNPPC related urological tumors include prostate and germ cell tumors [10].

Mean age of diagnosis in all cases of UUTC is 73 years [1]. LS associated urothelial cancers present at a younger age of 56 [2,8]. LS associated UC have an equal gender ratio and do not differ in high-grade potential compared to UC in the general population [11]. Our patient's age was 46 years at the time of diagnosis of UUTC. For staging and grading of UUTC, TNM classification and World Health Organization (WHO) histopathological grading are commonly used [3]. The five-year overall survival in UUTC is 95% for in-situ tumors, 89% in localized disease, 63% in node-positive patients and 17% in metastatic disease [3,6].

Surgical resection plays a crucial role in the treatment for UUTC. The extent of surgical management of UUTC depends on tumor grade and stage, and range from radical nephroureterectomy to nephron-sparing laparoscopic or ureteroscopic resection and/or ablation of the tumor mass and its proximal margins with lymph nodes [3,6]. Following surgery, locoregional failure is reported in 9–15% of patients with low grade and low stage disease, and in 30–50% of those with high grade and advanced disease [6]. Distal recurrences are possible, as one study showed that after nephroureterectomy, 36 of 82 patients (44%) subsequently had bladder cancer at a mean follow-up of 44 months [11]. This was demonstrated in our patient, who at the time of nephroureterectomy exhibited only localized spread and about three months later had evidence of metastases. Another study demonstrated 31.2% and 5.8% incidence rates of recurrent bladder tumours and contralateral UUTC tumors, respectively, after the diagnosis of ipsilateral UUTC [11].

Localized or systemic adjuvant chemotherapy and radiation therapy also depend on the tumor stage and grade [3,6]. For in-situ and localized tumors, chemotherapeutic agents typically used include BCG, mitomycin-C, thiotepa or Adriamycin [3]. These agents are administered by bladder instillation for either antegrade or retrograde exposure for brief periods [3]. For advanced metastatic disease or post-surgery positive margins or with lymph node involvement, cisplatin-based chemotherapy remains the standard of care [3]. For patients who are not candidates to receive cisplatin or have a poor response to it, as in the case of our patient, second-line chemotherapy treatment option include pembrolizumab, which is a novel humanized monoclonal antibody that targets PD-1 by acting as immune T-cell checkpoint inhibitor [12]. Recent studies show that immune checkpoint-blocking therapies have positive therapeutic outcomes for a series of human malignancies related to MMR deficient tumors, independent of underlying tumor type [13]. Another anti-PD1 agent, nivolumab, achieved complete remission of metastatic renal cell carcinoma with a positive mutation in MMR gene MLH1 [14]. Use of adjuvant
radiotherapy in advanced metastatic disease is nonconclusive [3,6]. Retrospective studies show chemotherapy in combination with radiotherapy have improved outcomes for treatment of advanced disease [3].

There are varying opinions on screening to urothelial carcinoma of LS patients. There is literature that recommends screening for urothelial malignancies in family relatives of patient’s with LS, initially with urinalysis, urine cytology, cystoscopy and upper tract imaging [5]. International Collaborative Group on HNPCC (ICG-HNPPC) recommends screening for malignancies of the urinary tract after 30-35 years, at one to two-year intervals, only if there is a known family history [5]. The screening tests include ultrasonography and urine analysis [5].

Another study proposes a cautious approach when screening for UC in LS due to screening tests having low sensitivity and increased false positives leading to invasive follow-up tests [7]. This study recommends formal guidelines for screening LS associated UC only after more research with clinical trials with meta-analysis of case reports to an HNPC registry [7]. Some opinions advocate screening for UC on a subset of LS cases that have certain characteristic mutations. For instance, LS cases with MSH2 mutation are at increased risk of UC and patients with this genetic mutation are recommended to have screening for UC [2,15]. There is research that recommends a combination of genetic mutations causing MSI and immunohistochemical (IHC) analysis for MMR protein expression in selected tumor tissue, supplemented by DNA sequencing to be used as metrics to pursue screening and genetic counseling [10]. Multiple studies recommend reflexive MMR IHC screening followed by MSI testing be included in diagnostic guidelines for all UUTC, similar to current MMR IHC screening recommendations for colorectal and endometrial cancers [16,17].

In UC associated with LS, MLH1 gene mutations are less commonly reported as compared to other LS genes. For instance, in a case study of 44 cases of urothelial carcinoma, 8/44 (18%) had negative expression of MLH1, while 25/44 (57%) had a negative expression of MSH2 [18]. Another study concluded that MLH1 and PMS2 testing had little utility in UUTC compared to testing MSH2 and/or MSH6 [2,15].

**Conclusion**

Based on previously published case reports, MLH1 mutation has a lower statistical probability of causing UC in LS as compared to other genes (e.g., MSH2). This case report presents an outlier case of MLH1 genetic mutation associated with UC in LS. Patients diagnosed at an early age UC should raise suspicion in the clinicians about the possibility of genetic factors and should query family history for other LS spectrum cancers and accordingly consider confirmatory tests for MMR genetic mutations. There is still a lack of consensus on formal screening guidelines for UC in family members of a patient diagnosed with LS syndrome. However, more recent studies favor screening guidelines and/or genetic counseling for UC risks in LS, similar to established screening guidelines for colorectal and endometrial cancers, at least within a subset of LS cases, depending on the characteristics of the mutated genes. This case report along with several other research studies demonstrate that anti-PD1 therapies have significant implications for several types of MMR deficient malignancies.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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**References**