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Organ-Preserving Management of Primary Lynch Syndrome–Associated High-Grade Upper Tract Urothelial Carcinoma Using Gemcitabine–Cisplatin and Pembrolizumab: First Reported Case Worldwide

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Abstract

Lynch syndrome (LS), caused by germline mismatch-repair mutations, increases the risk of upper tract urothelial carcinoma (UTUC), for which radical nephroureterectomy is the standard treatment. Non-surgical curative management has not been described previously. We report a 48-year-old man with MSH2-associated LS who presented with a 3.5 cm distal ureteric high-grade UTUC. To preserve renal function, multidisciplinary consensus favoured systemic therapy over surgery. He received gemcitabine–cisplatin for six cycles followed by pembrolizumab for two years, achieving complete metabolic response on PET-CT. He remains disease-free at one year. This case demonstrates successful organ-preserving treatment of hereditary UTUC.

Keywords: Lynch Syndrome; MSH2; Upper Tract Urothelial Carcinoma; Pembrolizumab; Gemcitabine; Cisplatin; Organ Preservation; Immunotherapy

Introduction

Lynch syndrome (LS) also known as hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant cancer predisposition syndrome resulting from germline mutations in DNA mismatch repair (MMR) genes commonly MLH1, MSH2, MSH6 and PMS2 [1]. Defective MMR function leads to microsatellite instability (MSI), genomic hypermutability and an increased risk of developing a spectrum of malignancies including colorectal, endometrial, ovarian, gastric and urothelial cancers. Among these, upper tract urothelial carcinoma (UTUC) represents a well-recognized but relatively uncommon extracolonic manifestation of LS with reported lifetime risk of approximately 2–4% [2].

The risk of urothelial malignancies in LS is strongly influenced by the underlying MMR gene mutation with MSH2 mutations most frequently associated with cancers of renal pelvis and ureter [3]. LS associated UTUC often presents at a younger age compared to sporadic cases and may exhibit aggressive pathological features including high grade and advanced stage at diagnosis. These tumours typically demonstrate MSI-high (MSI-H) status and loss of MMR protein expression which has important diagnostic, prognostic and therapeutic implications.

Radical nephroureterectomy (RNU) with bladder cuff excision remains the standard of care for high-grade or invasive UTUC [4]. While oncologically effective but this approach results in permanent loss of renal unit function and may significantly impact long term renal reserve. This is particularly relevant in patients with LS who are at increased risk for metachronous malignancies and may require future systemic therapies that are nephrotoxic or dependent on adequate renal function.

Advances in systemic therapy have transformed the management of advanced urothelial carcinoma. Platinum- based chemotherapy and more recently immune checkpoint inhibitors have shown substantial clinical benefit especially in tumours characterized by MMR deficiency and MSI-H status [5–7]. Immunotherapy has demonstrated durable responses across multiple LS-associated malignancies reflecting the heightened immunogenicity of these tumours. Apart from these developments the role of systemic therapy as an alternative to surgery in localized LS-associated UTUC has not been established. There are no reported cases describing successful

non-surgical curative management of primary UTUC in patients with Lynch syndrome which highlights a significant gap in existing literature.

Case Presentation

A 46-year-old male with confirmed diagnosis of Lynch syndrome due to a germline MSH2 mutation presented with a 3-month history of dull intermittent left loin pain. There were no associated lower urinary tract symptoms, gross hematuria, fever or other complaints. His has no prior malignancies or renal disease.

The patient had a significant family history suggestive of hereditary cancer. His mother had been diagnosed with colorectal carcinoma and two maternal uncles had developed Lynch syndrome associated malignancies including colorectal cancer and renal cell carcinoma. Genetic testing performed earlier as part of family screening had confirmed an MSH2 mutation and the patient was under regular surveillance.

On initial evaluation, physical examination was unremarkable and laboratory investigations including renal function tests and complete blood counts were within normal limits. There is no hematuria on Urinalysis.

Imaging findings

Ultrasonography of the abdomen demonstrated left sided hydroureteronephrosis. Contrast enhanced computed tomography (CT) of the kidneys, ureters and bladder revealed a 3.5-cm enhancing intraluminal lesion in the distal left ureter located approximately 6–7 cm proximal to the vesicoureteric junction. The lesion caused upstream ureteral dilatation but showed no evidence of perilesional fat stranding, periureteric invasion or regional lymphadenopathy. There were no synchronous bladder lesions or contralateral upper tract abnormalities. Fluorodeoxyglucose positron emission tomography–CT (FDG PET-CT) demonstrated intense metabolic activity within the distal ureteric lesion (SUVmax 8.4) with no evidence of distant metastases or nodal disease (Figures 1 and 2).

Diagnostic procedure

The patient underwent cystoscopy-revealed a normal bladder mucosa. Left ureteroscopy identified a friable, papillary lesion in the distal ureter causing partial luminal obstruction. Targeted biopsy was performed followed by endoscopic fulguration to relieve obstruction. Histopathological examination confirmed high grade urothelial carcinoma (Figures 3 and 4). Given the patient's known MSH2 mutation, the tumour was considered highly suggestive of mismatch repair deficient disease.

Management decision

Standard management with radical nephroureterectomy and bladder cuff excision was discussed. However, considering the patient's young age, confirmed Lynch syndrome, high lifetime risk of metachronous malignancies, preserved baseline renal function and strong preference for renal preservation, the case was reviewed in a multidisciplinary tumour board comprising urologists, medical oncologists, radiologists, pathologists and genetic counsellors. In view of the tumour's presumed MSI-H/MMR-deficient biology and absence of metastatic, a non-surgical organ preserving approach using systemic therapy was recommended after informed consent.

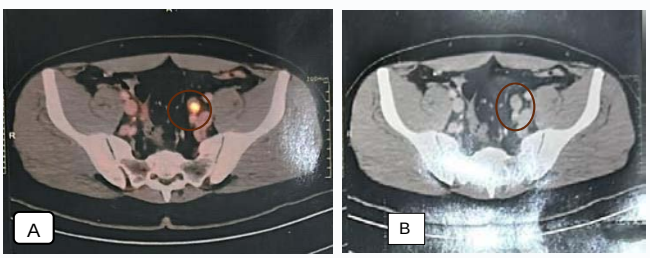

Figure 1: FDG avid heterogeneously enhancing lesion in left distal ureter.

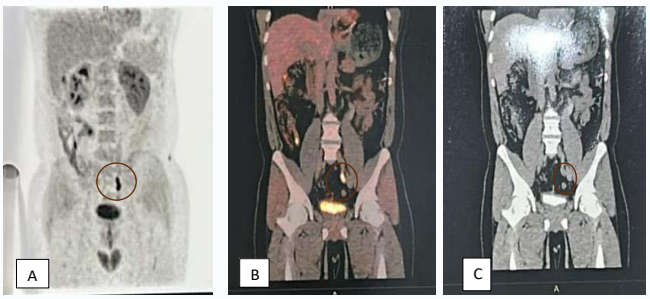

Figure 2: FDG avid heterogeneously enhancing lesion measuring 2.8- 3 cm approximately 7-8 cm from VUJ causing near complete occlusion with proximal dilatation

Systemic therapy

The patient received six cycles of combination chemotherapy with gemcitabine (1000 mg/m² on days 1 and 8) and cisplatin (70 mg/m² on day 1) administered every 21 days. The patient tolerated the treatment well with no grade 3 or 4 toxicities and renal function remained stable throughout chemotherapy. Following completion of chemotherapy, maintenance immunotherapy with pembrolizumab (200 mg intravenously every 3 weeks) was initiated and continued for a total duration of two years.

Outcome and follow-up

Interim FDG PET-CT performed at 6 months demonstrated complete metabolic resolution of the previously noted distal ureteric lesion with no new areas of abnormal uptake. Repeat imaging at 12 months confirmed sustained complete metabolic response with no evidence of locoregional recurrence or distant disease. Surveillance ureteroscopy revealed normal ureteric mucosa with no residual or recurrent tumour.

Last follow-up 12 months after completion of systemic therapy the patient remained disease-free with preserved renal function and excellent performance status.

Discussion

Urothelial carcinoma is a well-recognized extracolonic malignancy in Lynch syndrome (LS). It is the third most common cancer after colorectal and endometrial carcinoma [2, 3]. Among the mismatch repair (MMR) gene mutations associated with LS, MSH2 mutations confer the highest risk of urothelial malignancies with reported risks up to tenfold higher compared to other MMR gene defects [2, 3]. Upper tract urothelial carcinoma (UTUC) in LS often presents at a younger age is more frequently high grade and tends to involve the ureter rather than the renal pelvis differentiating it from sporadic UTUC [8, 10].

Radical nephroureterectomy (RNU) with bladder cuff excision remains the oncological standard for localized high-grade UTUC [4]. While effective in achieving local control, this approach

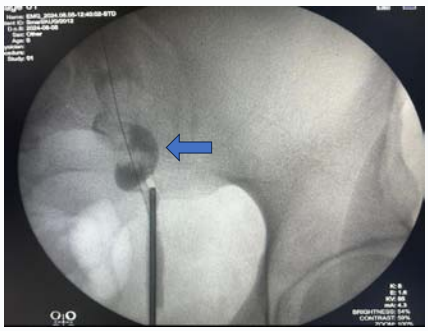

Figure 3: Left Retrograde pyelogram shows filling defect in left distal ureter.

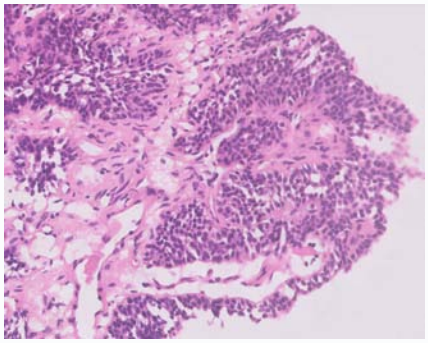

Figure 4: High grade urothelial carcinoma with squamous differentiation.

is associated with irreversible loss of renal function and may significantly limit future treatment options particularly in younger patients with hereditary cancer syndromes. Preservation of renal function is especially critical in LS patients who face a lifelong risk of metachronous malignancies and may require repeated exposure to systemic therapies or contrast-based imaging [4, 10].

Systemic therapy has traditionally been reserved for advanced, metastatic or recurrent urothelial carcinoma. Platinum based chemotherapy particularly gemcitabine–cisplatin constitutes the backbone of first line treatment in eligible patients demonstrating meaningful response rates and survival benefits [5, 7]. But its role as definitive therapy in localized UTUC has not been established due to concerns regarding durability of response and lack of prospective evidence. In LS-associated UTUC, tumour biology differs significantly from sporadic disease raising the possibility that systemic therapy may offer enhanced efficacy in this molecularly defined subgroup.

MMR deficiency and microsatellite instability-high (MSI-H) status result in a high tumour mutational burden, increased neoantigen formation and heightened immunogenicity rendering these tumours particularly susceptible to immune checkpoint inhibition [6, 7, 9]. Pembrolizumab has demonstrated robust and durable responses across multiple MSI-H solid tumours irrespective of tissue of origin leading to its tissue agnostic approval in this setting [9]. In urothelial carcinoma specifically checkpoint inhibitors have shown durable responses even in heavily pretreated patients [5–7].

Previous reports of LS associated UTUC treated with systemic therapy have largely involved metastatic, recurrent or post-surgical disease [10–13]. While chemotherapy responsiveness has been documented, complete and durable remissions without surgical resection have not been previously reported. Case reports describing immunotherapy responses in UTUC have typically involved metastatic settings or different MMR gene mutations such as MSH6 [11, 13]. In contrast, the present case demonstrates sustained complete remission of a primary localized high-grade UTUC in an MSH2 mutation carrier treated exclusively with systemic chemo-immunotherapy.

The favourable outcome observed in this patient likely reflects a synergistic effect between cytotoxic chemotherapy and immune checkpoint blockade. Chemotherapy may enhance antitumor immunity by inducing immunogenic cell death increasing antigen presentation, and modifying the tumour microenvironment thereby potentiating the efficacy of subsequent immunotherapy [7, 9]. The durable response achieved further supports the hypothesis that LS-associated UTUC represents a biologically distinct entity that may benefit from personalized, genetics informed treatment strategies.

This case challenges the traditional paradigm that radical surgery is mandatory for all cases of high-grade UTUC and suggests that in carefully selected patients, organ preserving systemic therapy may be a viable alternative. Such an approach should be considered only within a multidisciplinary framework with careful patient selection, rigorous surveillance and informed consent given the absence of long-term prospective data.

This report expands the current understanding of therapeutic possibilities in LS-associated UTUC and highlights the potential role of definitive systemic chemo-immunotherapy in achieving durable remission while preserving renal function. Further studies are required to define selection criteria, optimal treatment sequencing and long-term oncologic outcomes in this unique patient population.

Conclusion

This case represents the first documented instance of primary high-grade upper tract urothelial carcinoma in a patient with MSH2-mutated Lynch syndrome achieving complete and durable remission using systemic chemo immunotherapy without surgical intervention (Table 1). The sustained response observed following treatment with gemcitabine–cisplatin followed by pembrolizumab highlights the unique therapeutic vulnerability of mismatch repair deficient, microsatellite instability-high urothelial tumors.

The successful preservation of the affected renal unit in this

Table 1: Comparison of Reported Cases of Lynch Syndrome–Associated Upper Tract Urothelial Carcinoma (UTUC).

Author / Year	Country	LS Gene	Disease Stage	Treatment	Surgery	Outcome	Novelty
Mork et al., 2015 [10]	Norway	MSH2	Localized	RNU	Yes	Disease-free	Standard surgical case
Alanee et al., 2017 [11]	USA	MSH2	Metastatic	Cisplatin-based chemo	No	Partial response	Palliative setting
Shilpa et al., 2019 [12]	INDIA	MLH1	Localized	RNU+Chemo	Yes	NED	Post Surgical
Singla et al., 2021 [13]	UK	MSH6	Metastatic	Immunotherapy	No	Partial Response	Palliative intent
Present case (2025)	INDIA	MSH2	Primary localized (distal ureter)	Gemcitabine– Cisplatin + Pembrolizumab	No	Complete response (1 year)	First global report of curative, non-surgical management

young patient underscores the potential clinical significance of organ sparing strategies in hereditary cancer syndromes where long-term renal function is crucial for future surveillance and treatment of metachronous malignancies. This outcome questions the long-held belief that radical nephroureterectomy is required for all patients with high-grade UTUC and suggestive in carefully selected patients with favorable molecular features, systemic therapy may provide a curative organ-preserving alternative.

This case emphasizes the role of precision oncology and multidisciplinary decision making in tailoring treatment strategies based on genetic background, tumor biology and patient preferences. While radical surgery remains the standard of care for localized UTUC this report broadens the therapeutic paradigm by demonstrating that definitive systemic therapy can achieve durable disease control in select cases.

Prospective studies and collaborative registry data are needed to better define patient selection criteria, long-term oncologic outcomes and optimal surveillance protocols for non-surgical management of LS-associated UTUC. Until such data are available, this case provides proof of concept support for genetics informed, organ-preserving approaches in carefully monitored patients.

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