Lynch Syndrome: A Primer for Urologists and Panel Recommendations

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Purpose: Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, is a common genetic disease. The predisposition of patients with Lynch syndrome to urological cancer, particularly upper tract urothelial carcinoma, is underappreciated. Urologists may be involved in several aspects of care involving Lynch syndrome, including identifying undiagnosed patients, surveillance of those with established Lynch syndrome or screening family members, in addition to treating patients with Lynch syndrome in whom upper tract urothelial carcinoma develops. We sought to increase awareness in the urological community about Lynch syndrome and provide some guidance where little currently exists.

Materials and Methods: Using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement we reviewed the available published literature and guidelines from 1998 to 2014 on Lynch syndrome and its association with upper tract urothelial carcinoma. Recommendations based on the literature and the consensus of expert opinion are provided.

Results: No randomized or prospective study has been done to evaluate Lynch syndrome in the setting of urological cancer. All data were based on retrospective studies. Lynch syndrome is an autosomal dominant genetic disease caused by germline mutations in 4 mismatch repair genes, leading to the accumulation of DNA errors in microsatellite regions. Upper tract urothelial carcinoma develops in up to 28% of patients with known Lynch syndrome. The diagnosis of Lynch syndrome is established by clinical criteria, tumor tissue testing and genetic evaluation. Urologists should suspect Lynch syndrome when a patient with upper tract urothelial carcinoma presents before age 60 years or meets the 3-2-1 rule. Screening patients with Lynch syndrome for upper tract urothelial carcinoma presents a particular challenge. While no ideal screening test exists, at a minimum routine urinalysis is recommended using the American Urological Association guideline of 3 or more red blood cells per high power field as a trigger

Abbreviations and Acronyms

AUA = American Urological Association
CRC = colorectal carcinoma
CTU = computerized tomography urogram
HNPCC = hereditary nonpolyposis colorectal cancer
IHC = immunohistochemistry
LS = Lynch syndrome
MH = microhematuria
MMR = mismatch repair
MSI = microsatellite instability
MSI-PCR = MSI by PCR
NMP-22 = nuclear matrix protein-22
PCR = polymerase chain reaction
RBC/HPF = red blood cells per high power field
UA = urinalysis
UTUC = upper tract urothelial carcinoma

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for further assessment. Upper tract urothelial carcinoma associated with Lynch syndrome presents at a younger age than sporadic upper tract urothelial carcinoma. It shows a higher proportion of ureteral cancer with a female preponderance and a possible predisposition to bilaterality.

Conclusions: Lynch syndrome is a common genetic disease that is an underappreciated cause of upper tract urothelial carcinoma and possibly other urological cancers. Optimal screening for upper tract urothelial carcinoma in this population is unclear. Further study is needed to identify the best screening test and interval of testing. Urologists should consider routine tissue testing of de novo upper tract urothelial carcinoma tissue in individuals at risk.

Key Words: kidney neoplasms; ureteral neoplasms; colorectal neoplasms, hereditary nonpolyposis; carcinoma, transitional cell; DNA mismatch repair

Lynch syndrome, also called HNPCC, is the most common hereditary cause of colorectal and endometrial malignancies, accounting for approximately 1% to 3% of all colorectal cancers and 2% to 5% of endometrial cancers.[1] While colorectal cancer may be the most commonly recognized feature of families with LS, patients may present with a spectrum of other cancers, including endometrial, ovarian, urinary tract, stomach, small bowel, hepatobiliary, sebaceous gland and central nervous system neoplasms.[2] Health care providers have a vital role in helping identify families with LS so that they can undergo appropriate screening and preventive measures to decrease cancer risk. While gastroenterologists and colorectal surgeons are expected to encounter individuals with LS most frequently, other specialists should be aware of LS, including its presentation, diagnosis and management.

UTUC is considered a core cancer in LS with a reported lifetime risk of 2.9% overall but up to 28% depending on individual risk.[2] There is a lack of appreciation of the association of HNPCC with a wide variety of extracolonic tumors. Therefore, it is presumed that some hereditary cancers are misclassified as sporadic and the incidence is underestimated.

The urologist can have a key role in 3 potential areas, including 1) initial identification of a patient with undiagnosed LS who presents with UTUC, 2) surveillance for UTUC in patients with LS and family members, and 3) UTUC treatment in patients with known LS. In this review we provide an overview of LS for urologists, a framework for screening considerations in patients with UTUC and suspected LS, and the evaluation for UTUC in patients with known LS.

MATERIALS AND METHODS

We performed a database search for articles indexed in the PubMed® and MEDLINE® databases between 1998 and 2014. Key words included Lynch syndrome, urothelial cancer, ureter and kidney (renal). PRISMA[3] methodology was applied with select publications included in this review. Case reports, small patient series and nonEnglish language publications were excluded from study. Additionally, publications were vetted from collaborators in genetic, nonurology and urology associated subjects in particularly relevant cases. In all instances in this review individuals at risk are considered those with a de novo diagnosis of UTUC and not those with an initial diagnosis of bladder cancer. Recommendations based on the literature and expert opinion were developed by discussion and consensus.

RESULTS

A total of 49 publications were selected for review (fig. 1). The overwhelming majority of publications related to LS were based on retrospective analyses. Because no randomized or prospective study of the urological LS population was found, only a qualitative review was performed. Review results are presented as topics and questions relevant to the practicing urologist.

LS Genetics and Neoplasm Spectrum

LS is caused by germline mutations in the MMR genes *MLH1, MSH2* (and its modifier *EPCAM*), *MSH6* and *PMS2*. Pathogenic mutations in these genes lead to the accumulation of DNA errors in replicating cells, notably in microsatellite regions. Microsatellites are short repeating sequences of DNA that frequently serve as molecular markers in various genetic tests. MMR gene mutations are inherited in an autosomal dominant pattern and cause increased risk of a number of malignancies (fig. 2).

The spectrum of urinary tract tumors in individuals with LS includes primarily renal pelvis and ureteral tumors with potential added bladder susceptibility, although it is unclear whether these lesions are secondary to downstream seeding.[2,4–6] Specific gene mutations in LS appear to be associated with urinary tract cancer. Specifically the UTUC risk appears greater in individuals with *MSH2* mutations than in those with other MMR gene mutations.[4,5] There is also a potentially wide spectrum of susceptibility to urological cancer in LS,