Metachronous Bilateral Urothelial Carcinoma in a Patient with Hereditary Nonpolyposis Colorectal Cancer Syndrome - A Case Report

Abstract
We present a case of metachronous upper urinary transitional cell carcinoma in a 62 year old man found to have hereditary nonpolyposis colorectal cancer syndrome (HNPCC/Lynch syndrome). We then bring a short review of the literature.

Case Report
A 62-year-old man presented to our ward for evaluation of right hydronephrosis found on imaging performed for a new onset acute or chronic kidney disease evaluation. Medical history revealed a sub-total colectomy performed for colon cancer 8 years ago and subsequent chemotherapy. Ureteroscopy revealed an intraureteric papillary lesion found to be transitional cell carcinoma (TCC) T2 high grade (HG) on histology. The patient underwent a right radical nephroureterectomy. 3 months later he presented with new onset acute or chronic kidney failure. Computed Tomography (CT) revealed left hydronephrosis and a suspected tumor in the left pelvis. Multiple lesions and a huge renal pelvic tumor were found on left ureteroscopy. Histology revealed TCC HG disease. The patient underwent a left nephroureterectomy and radical cystectomy and was put on hemodialysis. Histology revealed a T3N1HG disease.

This patient's 52 year old younger sister presented later with right upper tract urothelial carcinoma (UTUC) in her right pelvis. Ureteroscopic biopsy revealed TCC T1HG disease. After receiving neoadjuvant chemotherapy (Gemcitabine + Cisplatinum) imaging showed a near to complete response in the renal pelvis and paraortic mass. She underwent a right nephroureterectomy with modified lymph dissection which showed no evidence of disease. Genetic investigation revealed a Q158X mutation on MSH2 gene consistent with the diagnosis of Lynch syndrome/HNPCC (hereditary nonpolyposis colorectal cancer). A family tree of the patients' family is shown in Figure 1. Yamada et al. [1] recently reported a similar case of metachronous upper tract TCC associated with hereditary nonpolyposis cancer (HNPCC) requiring radical surgery. Hubosky et al. [2] reported that of 13 HNPCC patients treated for upper tract TCC, 6 had bilateral disease.
Short Review of the Literature

In 1913 Warthin first described a hereditary pattern of carcinoma’s affecting several families. The susceptibility was particularly for lip, mouth, breast, stomach, intestine and uterus carcinoma’s [3]. It was not until a few decades later that Dr. Henry Lynch described families with predisposition to hereditary malignancy and brought the syndrome to the awareness of the medical community [4,5]. Due to his colossal contribution, the term “Lynch syndrome” is now more commonly used to describe HNPPC.

Lynch syndrome is a hereditary disease inherited in an autosomal dominant manner. The underlying defect involves the mismatch repair (MMR) system, comprised of 4 genes producing the MMR proteins: MLH1, MSH2, MSH6 and PMS2. These mutations result in microsatellite instability (MSI). Up to 70-90% of the cases are attributed to mutations in MLH1 and MSH2 [6-8]. MSH2 mutation seems to hold the highest risk factor for several cancer types including UTUC [9,10].

The most common manifestations are colon, Endometrial and ovarian cancers with prevalence of up to 70%, 40 and 11% respectively. Other manifestations include gastric, urothelial carcinoma, small bowel, hepatobiliary, pancreas, brain and sebaceous cancers with prevalence much lower ranging 3-13% [11]. UTUC has been reported to have up to 22 fold increased risk of occurring in Lynch syndrome individuals compared to the general population. The age of occurrence is substantially younger with a median of 56 years [12]. The revised Amsterdam criteria have become widely used to identify high risk families suitable for further genetic investigation. The criteria identify families with 3 closely related members of 2 generations with cancer types including UTUC [9,10].

Conclusion

UTUC is a lethal disease. High level of suspicion can lead to early diagnosis of Lynch syndrome and hence prompt early screening for different malignancies in order to improve survival.

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