Virchows Archiv

ORIGINAL ARTICLE
Published: 23 August 2023
Volume 483, pages 517–526, (2023)

Lynch syndrome-associated upper tract urothelial carcinoma frequently occurs in patients older than 60 years: an opportunity to revisit urology clinical guidelines

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PMID: 37612527
DOI: 10.1007/s00428-023-03626-2

Abstract

Upper tract urothelial carcinoma (UTUC) is the third most common malignancy associated with Lynch syndrome (LS). The current European urology guidelines recommend screening for LS in patients with UTUC up to the age of 60 years. In this study, we examined a cohort of patients with UTUC for potential association with LS in order to establish the sensitivity of current guidelines in detecting LS. A total of 180 patients with confirmed diagnosis of UTUC were enrolled in the study during a 12-year period (2010–2022). Loss of DNA-mismatch repair proteins (MMRp) expression was identified in 15/180 patients (8.3%). Germline analysis was eventually performed in 8 patients confirming LS in 5 patients (2.8%), including 4 germline mutations in *MSH6* and 1 germline mutation in *MSH2*. LS-related UTUC included 3 females and 2 males, with a mean age of 66.2 years (median 71 years, range 46–75 years). Four of five LS patients (all with *MSH6* mutation) were older than 65 years (mean age 71.3, median 72 years). Our findings indicate that LS-associated UTUCs can occur in patients with LS older than 60 years. In contrast to previous studies which used mainly highly pre-selected populations with already diagnosed LS, the most frequent mutation in our cohort involved *MSH6* gene. All *MSH6* mutation carriers were > 65 years, and UTUC was the first LS manifestation in 2/4 patients. Using current screening guidelines, a significant proportion of patients with LS-associated UTUC may be missed. We suggest universal immunohistochemical MMRp screening for all UTUCs, regardless of age and clinical history.

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