Stage IV perihilar cholangiocarcinoma with loss of expression of MSH2 and MSH6: hereditary cancer syndrome?

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Dear Editor,

We present the case of a 69-year-old male diagnosed with stage IV perihilar cholangiocarcinoma with loss of expression of MSH2 and MSH6 proteins, but somatic wild type MSH2 and MSH6 genes with Oncomine Comprehensive Assay (OCA) genomic sequencing panel. In his cancer family history, there was a maternal aunt with sigmoid colon adenocarcinoma also missing MSH2 and MSH6 protein expression (Fig. 1).

Discussion

Biliary tract tumors represent less than 1% of all cancer cases. Their molecular complexity makes it imperative to carry out genomic sequencing analysis. Focusing on our patient, the following diagnostic hypotheses were considered:

First hypothesis: Lynch syndrome. This autosomal dominant entity with incomplete penetrance is associated with a higher predisposition to develop colorectal and endometrial cancer, as well as tumors of the urinary tract, prostate, pancreas and bile ducts. In our case, Lynch syndrome could be originated from germline mutations in DNA repair genes, such as a large deletion in the EPCAM gene or the MSH2 gene, both of them not detectable using the OCA genomic sequencing panel. Additionally, Lynch syndrome could result from atypical germline mutations in DNA repair genes, such as inversions and translocations.

Second hypothesis: Lynch-like syndrome. Lynch-like syndrome may arise from germline mutations in the POLE or POLD1 genes, as well as biallelic germline mutations in the MUTYH gene, capable of generating secondary biallelic somatic mutations in DNA repair genes, leading to tumors with Lynch syndrome phenotype (1,2). However, the OCA genomic sequencing panel does not include the POLD1 and MUTYH genes.

Third hypothesis: sporadic tumors. Carcinogenesis could arise from biallelic somatic mutations in DNA repair genes (3), as well as biallelic somatic mutations in the POLE or POLD1 genes. Considering the personal and family cancer history of our patient, this hypothesis seemed unlikely.

Finally, due to the suspicion that the present case corresponded to a hereditary cancer syndrome, a germline study of the MSH2 gene was conducted using massive
sequencing and MLPA (Multiplex Ligation-dependent Probe Amplification). The result revealed a c.942+3A>T intron 5 MSH2 gene pathogenic mutation, a Lynch syndrome founder mutation in some populations, underlining the lack of technical detection for MSH2 intronic variants with tumor-only sequencing (4).

References
Fig. 1. Medical family tree based on the personal and family cancer history of our patient.