Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

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

Authors:
César Gutiérrez Pérez, Inmaculada Rodríguez Ledesma, Carmen Blanco Abad, Ana María López Muñoz, Irene Chivato Martín-Falquina, Mercedes Durán Domínguez, Enrique Lastra Aras

DOI: 10.17235/reed.2023.9724/2023
Link: PubMed (Epub ahead of print)

Please cite this article as:
Gutiérrez Pérez César, Rodríguez Ledesma Inmaculada, Blanco Abad Carmen, López Muñoz Ana María, Chivato Martín-Falquina Irene, Durán Domínguez Mercedes, Lastra Aras Enrique. Stage IV perihilar cholangiocarcinoma with loss of expression of MSH2 and MSH6: hereditary cancer syndrome?. Rev Esp Enferm Dig 2023. doi: 10.17235/reed.2023.9724/2023.

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

CC 9724 inglés

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

César Gutiérrez Pérez[1], Inmaculada Rodríguez Ledesma[1], Carmen Blanco Abad[1], Ana María López Muñoz[1] Irene Chivato Martín-Falquina[2], Mercedes Durán Domínguez[3], Enrique Lastra Aras[1]

Departments of [1]Medical Oncology and [2]Digestive Diseases. Hospital Universitario de Burgos (HUBU). Burgos, Spain. [3]Instituto de Biomedicina y Genética Molecular (IBGM). Universidad de Valladolid. Valladolid, Spain

Correspondence: César Gutiérrez Pérez
e-mail: cesargutierrezperez@hotmail.com

Author contributions: César Gutiérrez Pérez: conceptualization, investigation and writing (original draft, review and editing). Inmaculada Rodríguez Ledesma: methodology and project administration. Carmen Blanco Abad: formal analysis. Ana María López Muñoz: software*. Irene Chivato Martín-Falquina: data curation. Mercedes Durán Domínguez: resources. Enrique Lastra Aras: supervision, validation and visualization.*

Conflict of interest: the authors declare no conflict of interest.

Keywords: Cholangiocarcinoma. Genomics. Lynch syndrome.

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 according to the Oncomine Comprehensive Assay (OCA) genomic sequencing panel. Regarding cancer family history, there was a

maternal aunt with sigmoid colon adenocarcinoma also lacking 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. Regarding our patient, the following diagnostic hypotheses were considered:

- 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 originate from germline mutations in DNA repair genes, such as a large deletion in the EPCAM gene or the MSH2 gene, both of which are not detectable using the OCA genomic sequencing panel. In addition, Lynch syndrome could result from atypical germline mutations in DNA repair genes, such as inversions and translocations (2).
- 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 (3).
- 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 was associated with a hereditary cancer syndrome, a germline study of the MSH2 gene was performed using massive sequencing and multiplex ligation-dependent probe amplification (MLPA). 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

1. Morak M, Heidenreich B, Keller G, et al. Biallelic MUTYH mutations can mimic Lynch syndrome. Eur J Hum Genet 2014;22(11):1334-7. DOI: 10.1038/ejhg.2014.15

2. Castillejo A, Vargas G, Castillejo MI, et al. Prevalence of germline MUTYH mutations among Lynch-like syndrome patients. Eur J Cancer 2014;50(13):2241-50. DOI: 10.1016/j.ejca.2014.05.022

3. Mensenkamp AR, Vogelaar IP, van Zelst-Stams WA, et al. Somatic mutations in MLH1 and MSH2 are a frequent cause of mismatch-repair deficiency in Lynch syndrome-like tumors. Gastroenterology 2014;146(3):643-6.e8. DOI: 10.1053/j.gastro.2013.12.002

4. Terraf P, Pareja F, Brown DN, et al. Comprehensive assessment of germline pathogenic variant detection in tumor-only sequencing. Ann Oncol 2022;33(4):426-33. DOI: 10.1016/j.annonc.2022.01.006

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

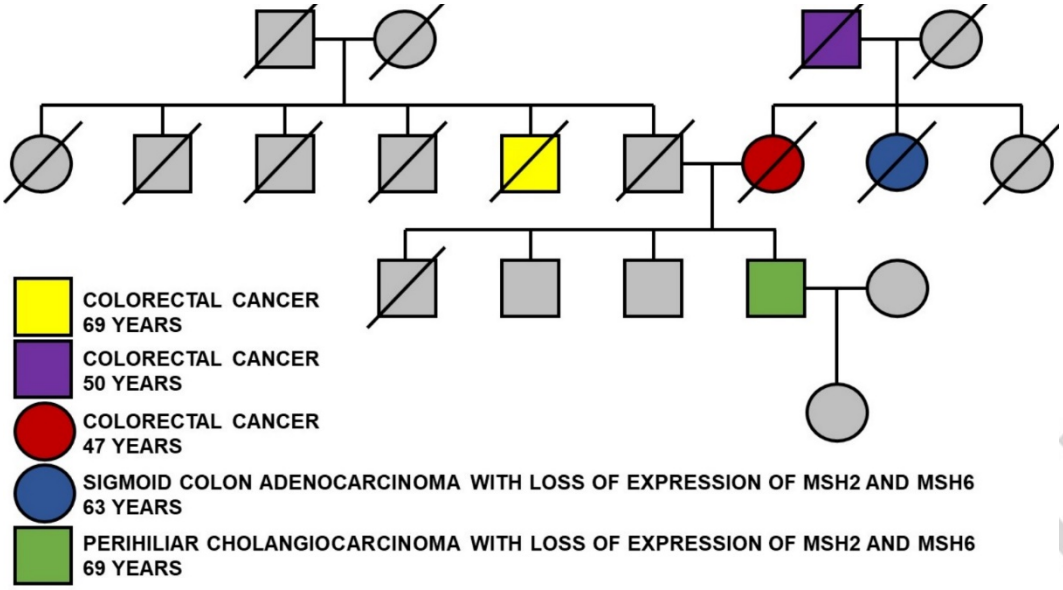

Fig. 1. Medical family tree based on the personal and family cancer history of our patient.