Demetra Georgiou, MSc
Clinical Genetics, London North West University Healthcare NHS, HA1 3UJ
Trust and Clinical Genetics, Guy's and St Thomas' NHS Foundation Trust, SE1 9RT
E-mail address: demetra.georgiou@nhs.net

Vicki Kiesel, MSc
Angela F. Brady PhD
Clinical Genetics, London North West University Healthcare NHS, HA1 3UJ

Kevin Monahan, PhD
Imperial College London and, Chelsea and Westminster Hospitals NHS Trust, SW10 9NH

https://doi.org/10.1016/j.humpath.2019.04.015

References

[1] Hemminger JA, Pearlman R, Haraldsdottir S, et al. Histology of colorectal adenocarcinoma with double somatic mismatch-repair mutations is indistinguishable from those caused by Lynch syndrome. Hum Pathol 2018;78:125-30.
[2] Mas-Moya J, Dudley B, Brand RE, et al. Clinicopathological comparison of colorectal and endometrial carcinomas in patients with lynch-like syndrome versus patients with lynch syndrome. Hum Pathol 2015;46:1616-25.
[3] Carethers JM, Stoffel EM. Lynch syndrome and Lynch syndrome mimics: the growing complex landscape of hereditary colon cancer. World J Gastroenterol 2015;21:9253.
[4] Rodríguez–Soler M, Pérez–Carbonell L, Guarinos C, et al. Risk of cancer in cases of suspected lynch syndrome without germline mutation. Gastroenterology 2013;144:926-32.
[5] Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010;59:666-89.

"Histology of colorectal adenocarcinoma with double somatic mismatch-repair mutations is indistinguishable from those caused by Lynch syndrome"—reply

Dear Editor,

Thank you to Drs Demetra Georgiou, Vicki Kiesel, Angela F. Brady, and Kevin Monahan for sharing their experiences with Lynch-like syndrome in the United Kingdom in response to our article [1]. We appreciate the difficulty of knowing how to manage patients with unexplained mismatch repair deficiency (dMMR) appropriately and found the authors' data very interesting. One detail we would like to note is the difference between management recommendations in the United Kingdom and the United States. The authors say that "in the UK, [patients with unexplained dMMR] and their first degree relatives are eligible for 2 yearly colonoscopy as per LS guidelines [2]." In the United States, current management guidelines from the National Comprehensive Cancer Network's Genetic/Familial High-Risk Assessment: Colorectal version 1.2018 state that "if double somatic [MMR] mutations are identified [via tumor sequencing] or if [tumor sequencing] does not help clarify the result, *it is recommended that these patients and their close relatives be managed based on their family history and NOT as if they have Lynch syndrome.* Regardless of the results of tumor sequencing, these patients and their close relatives should be managed based on their family history and NOT as if they have Lynch syndrome unless their family history warrants it" [3]. One of the biggest factors contributing to the shift from managing dMMR patients as if they had Lynch syndrome without an identified germline mutation to managing them based on their family history was the discovery that 45%-69% of patients with unexplained dMMR actually have double somatic mutations, not a missed germline mutation [4-7].

We would also like to update that although we found no histological differences between colorectal tumors due to Lynch syndrome or double somatic MMR mutations, we have found clinical differences between the 2 patient groups. We recently published the characteristics that differentiate colorectal cancer patients with Lynch syndrome from those with double somatic MMR mutations or unexplained dMMR [8]. We found that patients with double somatic MMR mutations were more likely to have loss of MLH1/PMS2 proteins in their tumor, and patients with Lynch syndrome were more likely to have a family history of Lynch-associated cancers and/or a personal history of multiple primary cancers [8]. We hope that our new publication will help to provide further insight into a complex clinical situation.

Rachel Pearlman, MS, LGC
Department of Internal Medicine, Division of Human Genetics, The Ohio State University Wexner Medical Center, Columbus, OH

Jessica Hemminger, MD
Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, OH

Heather Hampel, MS, LGC
Department of Internal Medicine, Division of Human Genetics, The Ohio State University Wexner Medical Center, Columbus, OH

Wendy L. Frankel, MD
Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, OH
Corresponding author.
E-mail address: wendy.frankel@osumc.edu

https://doi.org/10.1016/j.humpath.2019.04.017

References

[1] Hemminger JA, Pearlman R, Haraldsdottir S, et al. Histology of colorectal adenocarcinoma with double somatic mismatch-repair mutations is indistinguishable from those caused by lynch syndrome. Hum Pathol 2018;78:125-30.

[2] Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010;59:666-89.

[3] National Comprehensive Cancer. Network Genetic/familial high-risk assessment: colorectal. Version 1.2018. NCCN guidelines for detection, prevention, & risk reduction. Clinical practice guidelines in oncology. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf; 2018.

[4] Sourrouille I, Coulet F, Lefevre JH, et al. Somatic mosaicism and double somatic hits can lead to MSI colorectal tumors. Familial Cancer 2013;12:27-33.

[5] 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;146:643-6 [e8].

[6] Geurts-Giele WR, Leenen CH, Dubbink HJ, et al. Somatic aberrations of mismatch repair genes as a cause of microsatellite-unstable cancers. J Pathol 2014;234:548-59.

[7] Haraldsdottir S, Hampel H, Tomsic J, et al. Colon and endometrial cancers with mismatch repair deficiency can arise from somatic, rather than germline, mutations. Gastroenterology 2014;147:1308-16 e1301.

[8] Pearlman R, Haraldsdottir S, de la Chapelle A, et al. Clinical characteristics of patients with colorectal cancer with double somatic mismatch repair mutations compared with lynch syndrome. J Med Genet 2019, PMID 30877237.