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CLINICAL VIGNETTE

Synchronous MSI-H Colon Cancer and Follicular Lymphoma in a 54-Year-Old Male

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A 54-year-old male had his first colonoscopy screening before age 40 because of family history of colon cancer in his maternal grandmother. Initial colonoscopy was reportedly normal. His last colonoscopy was greater than 10 years ago, after he noted a change in stool caliber. Colonoscopy revealed a nearly obstructive large fungating mass in the sigmoid colon which on biopsy was a moderately differentiated invasive adenocarcinoma with focal mucinous features. KRAS mutated, BRAF wildtype with deficient mismatch repair proteins (dMMR) showing loss of nuclear expression of PMS2, compatible with microsatellite instability high (MSI-H). Staging CT scans of chest, abdomen and pelvis showed a 5 cm area of thickened sigmoid colon as well as a large 8.8 x 6.7 cm mesenteric mass presumed to a nodal conglomerate. There was also a sclerotic T4 lesion suspicious for boney island vs osseous metastasis and 1.5 cm paraesophageal lymph node.

After consultation with surgical oncology, he was not felt to be at risk for imminent obstruction, and based on what appeared to be stage IV metastatic disease his treatment was based on Keynote-177 for MSI-H colon cancer.[1] After 6 cycles of pembroluzimab there was minimal change in his mesenteric adenopathy, and small volume mediastinal adenopathy but improvement in the colonic thickening. The questionable T4 lesion was not felt to be malignant. Given the discordant response, CT guided core needle biopsy of mesenteric mass was performed and revealed follicular lymphoma, grade 2 of 3, with immunohistochemistry (IHC) showing CD10, CD19, CD20, PAX5, BCL2 and BCL6 positivity, with similar immunophenotype by flow cytometry. Ki-67 was 15%, EBER-ISH was negative and FISH confirmed t(14;18). Following biopsy, he remained on pembroluzimab and underwent a sigmoid colectomy and lymph node sampling as well as surgical biopsy of mesenteric mass, which showed complete response in the sigmoid colon. Acellular mucin and biopsy tattoo were identified in surgical specimen confirming complete response. All 22 sampled lymph nodes were negative. Surgical biopsy of mesenteric mass again confirmed grade 2 follicular lymphoma.

This patient has several interesting points of discussion. Although the role of immunotherapy is well established in advanced/palliative treatments adjuvant or neoadjuvant is not well defined. The literature includes case reports with responses in advanced rectal cancer and metastatic colon cancer. The NCCN panel lists it as the preferred approach in patients with pT4 disease, unresectable with locally advanced or oligometastatic disease. This population is still initially managed surgically in MMR proficient disease.[2-5] Because our patient had a complete response, optimal duration of therapy needs to be defined. We know that dMMR/MSI-H has a ~40% response rate in advanced and metastatic disease with 11% complete response rate. In Keynote-177 patients were treated for two years. This is similar to other check point inhibitor clinical trials of advanced metastatic disease.[1] In malignancies like triple negative breast cancer and malignant melanoma where adjuvant pembroluzimab is approved, duration is usually 1 year total in the absence of immune related adverse events.[6,7]

This case illustrates efficacy of immunotherapy, as well as discussion of presumed metastatic disease as opposed to what we now know is synchronous or metachronous primary malignancies. We do not know how long he had the follicular lymphoma prior to diagnosis. The patient was initially informed that he had incurable metastatic colon cancer, with treatment options and prognosis. It is not common practice to document stage IV disease pathologically with highly suspicious imaging and tissue biopsy based on least invasive method. This patient still has an incurable malignancy, with Stage IIIA follicular lymphoma, in addition to his stage II colon cancer, but his overall prognosis differs by years.

In our practice we find increasing number of patients with synchronous primary malignancies similar to this case. The number of multiple primary malignancies ranges from 2-17%.[8] We speculate that frequency would be highest in malignancies that are smoking related and/or have genetic predispositions. Our patient underwent germline testing, given his age and dMMR to rule out Lynch syndrome, which is a variant of undermined significance in MLH1. Interesting MMR testing showed loss of nuclear expression of PMS2, which infers a somatic loss, with intact nuclear expression of MLH1. The role in our patient's colon cancer is unknown but may not be pathologic.

All indolent lymphomas including follicular lymphoma impact tumor immuno-surveillance.[9] Presumably having follicular lymphoma for an unknown duration prior to diagnosis increased risk for a second primary cancer, in this case colon cancer. A large population studies in the Netherlands from 1989-2018 reported 20-year risk of a secondary malignancy as high as 26%. The risk may be higher because they included squamous skin cancers.[10]

A thorough discussion with patient, we presume that his follicular lymphoma contributed to his risk of developing colon

cancer. Although that would not necessarily change how we managed his colon cancer care in the future, we elected to treat as if this was adjuvant with anticipated 1 year duration of therapy. We adopted a watch and wait approach to his follicular lymphoma, but given his age, size and location of his lymphoma would have a low threshold for therapy. This patient illustrates that particularly in younger, healthier patients. pathologic confirmation of stage IV disease can alter therapy. There should be a low threshold for biopsy of additional sites of disease.

REFERENCES

1. **André T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, Garcia-Carbonero R, Benavides M, Gibbs P, de la Fouchardiere C, Rivera F, Elez E, Bendell J, Le DT, Yoshino T, Van Cutsem E, Yang P, Farooqui MZH, Marinello P, Diaz LA Jr; KEYNOTE-177 Investigators**. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med*. 2020 Dec 3;383(23):2207-2218. doi: 10.1056/NEJMoa2017699. PMID: 33264544.
2. **Zhang J, Cai J, Deng Y, Wang H**. Complete response in patients with locally advanced rectal cancer after neoadjuvant treatment with nivolumab. *Oncoimmunology*. 2019 Sep 19;8(12):e1663108. doi: 10.1080/2162402X.2019.1663108. PMID: 31741760; PMCID: PMC6844302.
3. **Demisse R, Damle N, Kim E, Gong J, Fakih M, Eng C, Oesterich L, McKenny M, Ji J, Liu J, Louie R, Tam K, Gholami S, Halabi W, Monjazeb A, Dayyani F, Cho M**. Neoadjuvant Immunotherapy-Based Systemic Treatment in MMR-Deficient or MSI-High Rectal Cancer: Case Series. *J Natl Compr Canc Netw*. 2020 Jul;18(7):798-804. doi: 10.6004/jnccn.2020.7558. PMID: 32634770.
4. **Baimas-George M, Baker E, Kamionek M, Salmon JS, Sastry A, Levi D, Vrochides D**. A Complete Pathological Response to Pembrolizumab following ex vivo Liver Resection in a Patient with Colorectal Liver Metastases. *Chemotherapy*. 2018 Apr 5;63(2):90-94. doi: 10.1159/000487814. Epub ahead of print. PMID: 29621772.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Colon Cancer Version 1.2024. Jan 29, 2024. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1428.
6. **Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, Haydon A, Lichinitser M, Khattak A, Carlino MS, Sandhu S, Larkin J, Puig S, Ascierto PA, Rutkowski P, Schadendorf D, Koornstra R, Hernandez-Aya L, Maio M, van den Eertwegh AJM, Grob JJ, Gutzmer R, Jamal R, Lorigan P, Ibrahim N, Marreaud S, van Akkooi ACJ, Suciu S, Robert C**. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *N Engl J Med*. 2018 May 10;378(19):1789-1801. doi: 10.1056/NEJMoa1802357. Epub 2018 Apr 15. PMID: 29658430.
7. **Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J; KEYNOTE-522 Investigators**. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med*. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549. PMID: 32101663.
8. **Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T, Omlin A**. Multiple primary tumours: challenges and approaches, a review. *ESMO Open*. 2017 May 2;2(2):e000172. doi: 10.1136/esmoopen-2017-000172. PMID: 28761745; PMCID: PMC5519797.
9. **Morton LM, Curtis RE, Linet MS, Bluhm EC, Tucker MA, Caporaso N, Ries LA, Fraumeni JF Jr**. Second malignancy risks after non-Hodgkin's lymphoma and chronic lymphocytic leukemia: differences by lymphoma subtype. *J Clin Oncol*. 2010 Nov 20;28(33):4935-44. doi: 10.1200/JCO.2010.29.1112. Epub 2010 Oct 12. PMID: 20940199; PMCID: PMC3020697.
10. **Dinnessen MAW, Visser O, Tonino SH, Posthuma EFM, Blijlevens NMA, Kersten MJ, Lugtenburg PJ, Dinmohamed AG**. Risk of second primary malignancies in patients with follicular lymphoma: a population-based study in the Netherlands, 1989-2018. *Blood Cancer J*. 2021 Nov 13;11(11):179. doi: 10.1038/s41408-021-00574-5. PMID: 34775466; PMCID: PMC8590687.