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LETTER TO THE EDITOR

Which occurs first, ARID1A inactivation or microsatellite instability?: A comment to Yamamoto et al. (2024)

Dear Editor,

I read with great interest the article by Yamamoto et al. titled "Microsatellite Instability: A 2024 Update" published recently in *Cancer Science*.[1] Microsatellite instability (MSI) is gaining more interest, as it is considered a biomarker to determine the eligibility for immune checkpoint inhibitors in advanced cancer patients. In the middle of this article, I found that the authors concluded that ARID1A mutation or inactivation is a driver of MSI. Currently, this view seems to gain more ground. As the authors said, ARID1A knockout induced aberrant DNA methylation of CpG sites, suggesting ARID1A inactivation as one of the potential mechanisms of CpG island methylator phenotype induction.[2] Recently, using a proteomic screen, Shen et al.[3] found that ARID1A recruits the MMR protein MSH2 to chromatin during DNA replication and promotes MMR. Therefore, ARID1A inactivation compromises MMR, increases mutagenesis, and is correlated with an MSI signature.[3]

However, according to the original report by Wang et al.,[4] which discovered the close association of ARID1A mutation with MSI and Epstein–Barr virus (EBV) molecular subtypes in gastric cancer, ARID1A mutations often consist of indels involving short mononucleotide repeats of C or G, suggesting that they arise from MSI stemming from mismatch repair (MMR) defects. Then, which occurs first, ARID1A inactivation or MSI? Interestingly, one can glimpse the answer in the pathologic specimen.

The unconventional part of ARID1A inactivation is that it is sometimes subclonal and is well appreciated by using immunohistochemistry.[5] As a pathologist, I have witnessed subclonal ARID1A deficiency especially in MSI gastric cancers (Figure 1A). This phenomenon is also observed in EBV-associated gastric cancers (Figure 1B). The ARID1A deficiency in subclonal cancer cells strongly suggests that ARID1A inactivation occurred later in cells with MLH1 loss or in EBV-positive cancer cells. In support of this, I saw a small lesion with subclonal ARID1A loss in MLH1-deficient tumors (Figure 1C). However, early, subclonal MLH1 loss does not come with ARID1A deficiency (Figure 1D), which strongly opposes the concept that ARID1A deficiency induces MSI. In support of my findings, a recent study by Xu and colleagues[6] revealed that gastric cancer with MSI has a high level of ARID1A indel mutations at microsatellite regions, whereas the majority of ARID1A indel mutations occur at microsatellite-free regions in other molecular subtypes.

Furthermore, I have often observed that subclonal ARID1A deficiency in MSI gastric cancer matches deeply infiltrating portions or lymphovascular invasion, in contrast to the surrounding areas (Figure 2A). In addition, tumor differentiation is poorer in subclonal ARID1A-deficient regions (Figure 2A, right). This pattern is also observed in EBV-associated cancer, where ARID1A deficiency is found only in the deeply invading cancer portion that reaches the proper muscle layer, while the surrounding ARID1A-proficient cancer cells remain in the mucosa (Figure 2B). These compelling pathological images indicate that subclonal ARID1A inactivation develops later in MSI- or EBV-associated cancer cells and phenotypically becomes more aggressive (Figure 2C).

The question of causality—whether ARID1A inactivation leads to MSI or vice versa—resembles the classic conundrum of the chicken and the egg. Similarly, it is very challenging to elucidate the sequence of genetic events in the process of tumorigenesis, especially in the absence of precursor lesions that develop in a proper stepwise fashion. However, the beauty of ARID1A which is inactivated subclonally helps to clear the order of genetic incidences in gastric cancer. Nevertheless, I do not insist that there is no way that ARID1A inactivation leads to MSI in all cancer types, as ARID1A may be inactivated in a tissue- or cell-state-dependent manner. In summary, I believe that the pathological perspective I have offered here can provide a profound insight for readers to have a balanced view on this matter.

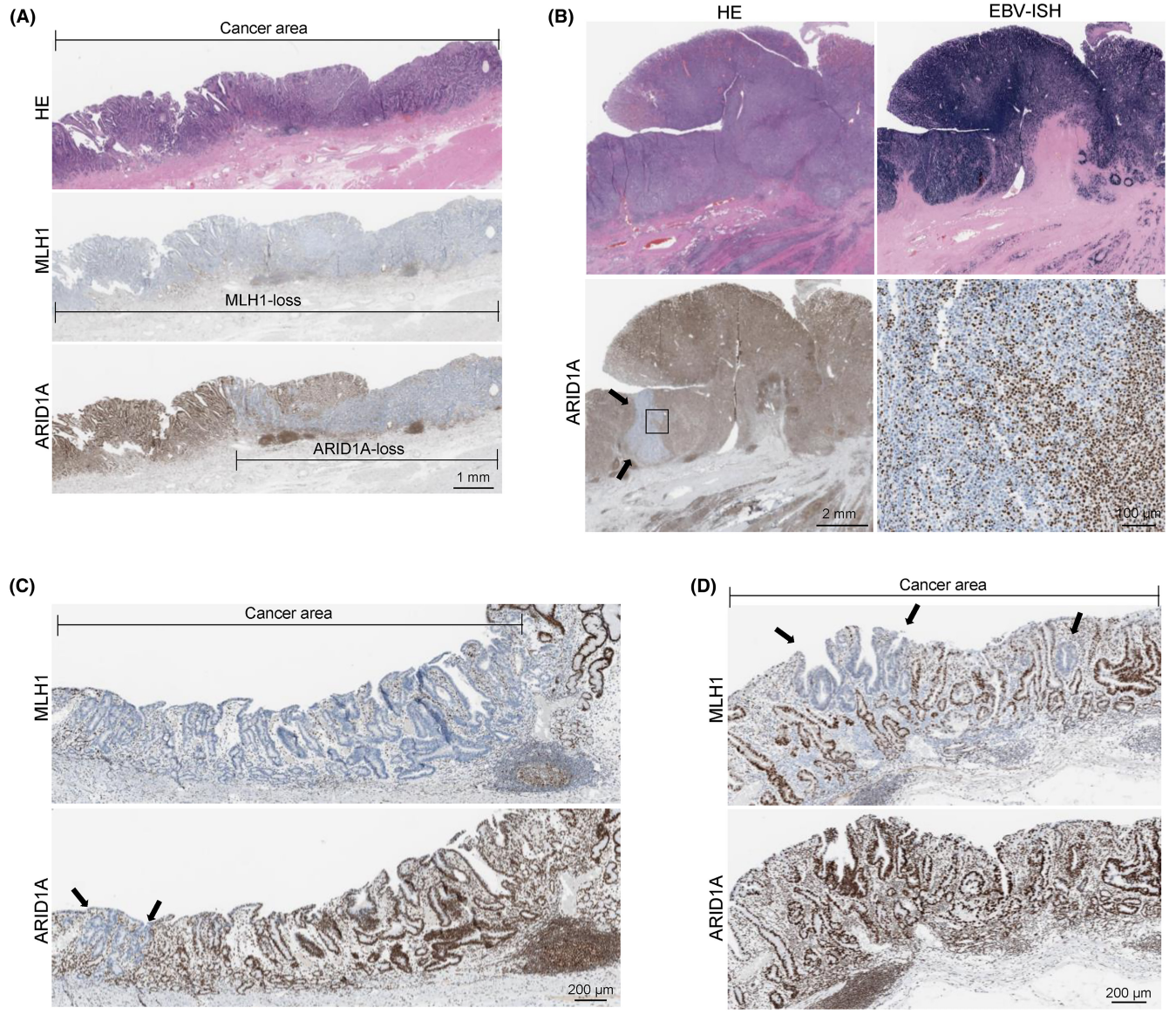

FIGURE 1 Subclonal ARID1A deficiency is found in (A) microsatellite instability (MSI)- or (B) Epstein–Barr virus (EBV)-associated gastric cancer. A small, early lesion (arrow) with ARID1A loss is found in MLH1-deficient tumors (C), whereas subclonal MLH1 loss (arrow) does not accompany ARID1A loss (D).

AUTHOR CONTRIBUTIONS

Dakeun Lee: Conceptualization; data curation; visualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

ETHICS STATEMENT

Approval of the research protocol by an Institutional Reviewer Board: This research was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-BMR-KSP-18-510).
Informed Consent: N/A.
Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

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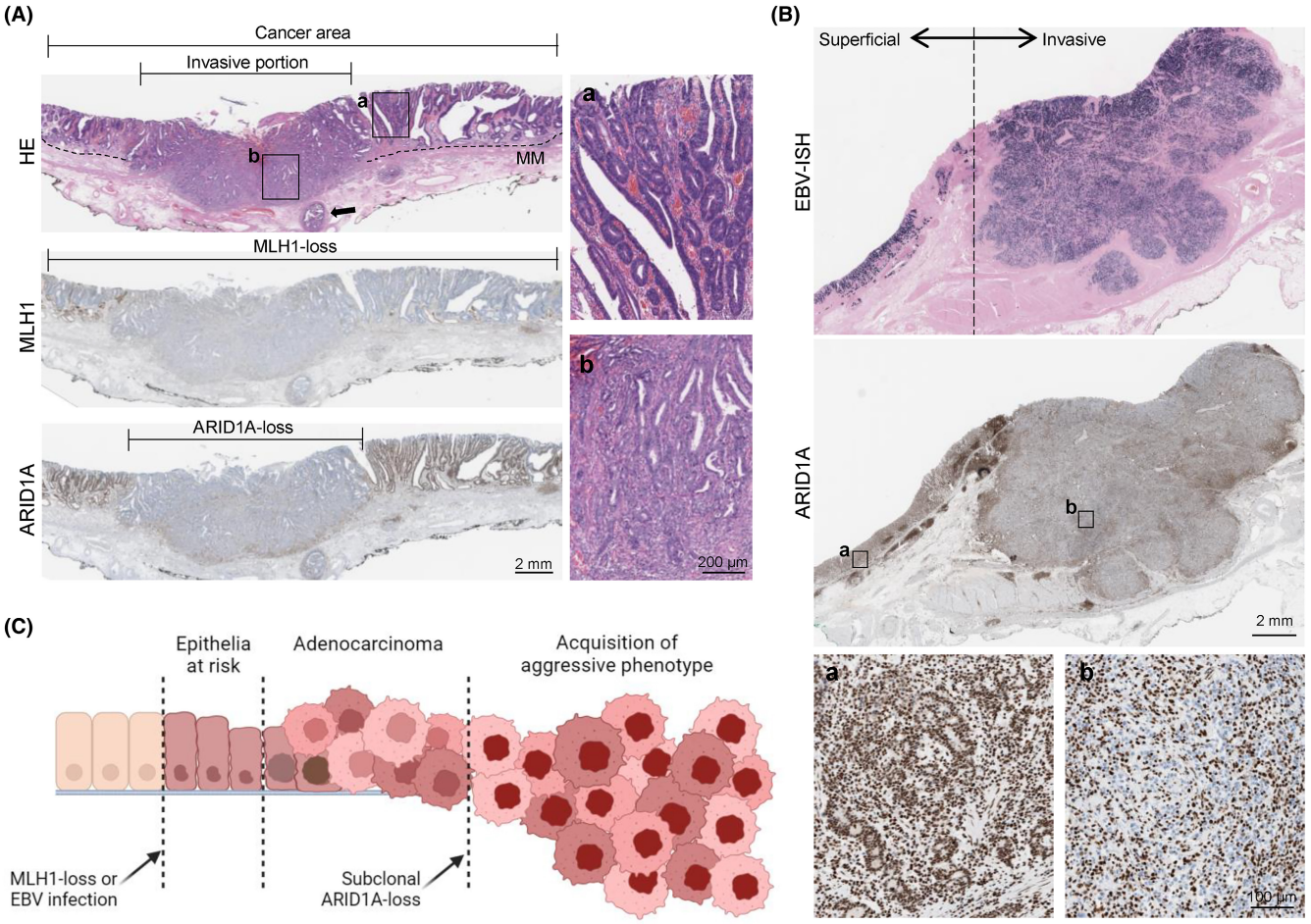

FIGURE 2 Subclonal ARID1A deficiency corresponds to the deeply infiltrating, aggressive cancer region in gastric cancer with microsatellite instability (MSI) (A) or Epstein–Barr virus (EBV) (B). Arrow indicates lymphovascular invasion. MM, mucularis mucosa. Collectively, ARID1A deficiency occurs later in MSI- or EBV-associated cancer, and the cancer seems to acquire an aggressive phenotype after subclonal ARID1A inactivation (C). This image was created with Biorender.com.

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REFERENCES

1. Yamamoto H, Watanabe Y, Arai H, Umemoto K, Tateishi K, Sunakawa Y. Microsatellite instability: a 2024 update. *Cancer Sci*. 2024;115(6):1738-1748.
2. Yamada H, Takeshima H, Fujiki R, et al. ARID1A loss-of-function induces CpG Island methylator phenotype. *Cancer Lett*. 2022;532:215587.
3. Shen J, Ju Z, Zhao W, et al. ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade. *Nat Med*. 2018;24(5):556-562.
4. Wang K, Kan J, Yuen ST, et al. Exome sequencing identifies frequent mutation of ARID1A in molecular subtypes of gastric cancer. *Nat Genet*. 2011;43(12):1219-1223.
5. Kim YB, Ham IH, Hur H, Lee D. Various ARID1A expression patterns and their clinical significance in gastric cancers. *Hum Pathol*. 2016;49:61-70.
6. Xu C, Huang KK, Law JH, et al. Comprehensive molecular phenotyping of ARID1A-deficient gastric cancer reveals pervasive epigenomic reprogramming and therapeutic opportunities. *Gut*. 2023;72(9):1651-1663.