Clinical Case Report

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Exploring potential treatment opportunities in a head and neck tumor patient with AdCC

A novel germline ERCC2 mutation case report

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Abstract

Rationale: Adenoid cystic carcinoma (AdCC) is an invasive head and neck malignancy characterized by unpredictable growth, extensive perineural invasion, a high rates of metastasis, and poor survival rates. Genetic alterations, including *MYB-NFIB* and *MYBL1-NFIB* fusions, and mutations within the Notch signaling and DNA damage repair pathways, have been identified.

Patient concerns: A 58-year-old female presented with a space-occupying lesion of the anterior cranial fossa floor during a physical examination and sought further consultation in July 2022.

In our case, a 58-year-old woman was incidentally found to have an anterior cranial fossa lesion during a routine physical examination, which was subsequently confirmed as AdCC following postoperative immunohistochemistry.

Diagnoses: Based on these imaging and histopathological findings, a diagnosis of AdCC was established. Integrating the genetic test results, the case was diagnosed as MYB or MYBL1 fusion-negative AdCC. This case report highlights a rare molecular signature of *ERCC2* and *BRCA2* inactivation in AdCC, in the absence of *MYB* or *MYBL1* fusions.

Interventions: The patient underwent postoperative radiotherapy (RT) to the primary site approximately 2.5 months postsurgery. The concurrent presence of germline ERCC2 and somatic BRCA2 mutations offers novel insights into potential treatment strategies for this rare malignancy.

Outcomes: To date, no recurrence has been observed during follow-up.

Lessons: We found a novel germline *ERCC2* mutation and somatic *BRCA2* mutation in a patient with AdCC. Our findings expand the molecular landscape of rare *MYB* or *MYBL1* fusion-negative AdCC patients and provide a potential therapeutic strategy for this rare head and neck tumor.

Abbreviations: AdCC = adenoid cystic carcinoma, DDR = DNA damage repair.

Keywords: adenoid cystic carcinoma, chemotherapy, DDR pathway, *ERCC2*, PARPi

1. Introduction

Adenoid cystic carcinoma (AdCC) is an invasive carcinoma occurring in the head and neck region, characterized by unpredictable growth, extensive perineural invasion, a high rates of metastasis, and consequently, a low survival rate.[1] Surgical intervention and radiotherapy are the primary treatment strategies for AdCC, with chemotherapy, targeted therapy, and immunotherapy also being utilized to enhance patient survival.[2] Genetically, *MYB-NFIB* and *MYBL1-NFIB* alterations are common molecular event in AdCC, identified in 16% to 100% of cases,[3] with preclinical studies targeting these alterations showing promising results.[4] Furthermore, molecular mutations in Notch signal pathway and DNA damage repair (DDR) pathway have been discovered due to the increased application of whole exome sequencing.[5] AdCC has not yet identified a definitive genetic susceptibility gene. However, germline mutations in *BRCA1/2*[6] and gene involved in DNA double-strand repair[5] may elevate the risk of AdCC. The association between mutations in cancer risk gene and AdCC warrants further investigation. In the era of personalized medicine, identifying comprehensive molecular profiles that can inform treatment decisions is crucial. We report a novel germline *ERCC2* mutation and a somatic *BRCA2* mutation in a patient with AdCC, enriching the mutational landscape of AdCC and offering insights into precision therapy.

Written informed consent were obtained from all the participants and legally authorized guardian's of patient for publication of this case report.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Written informed consent to participate in this study was provided by the participant's legal guardian.

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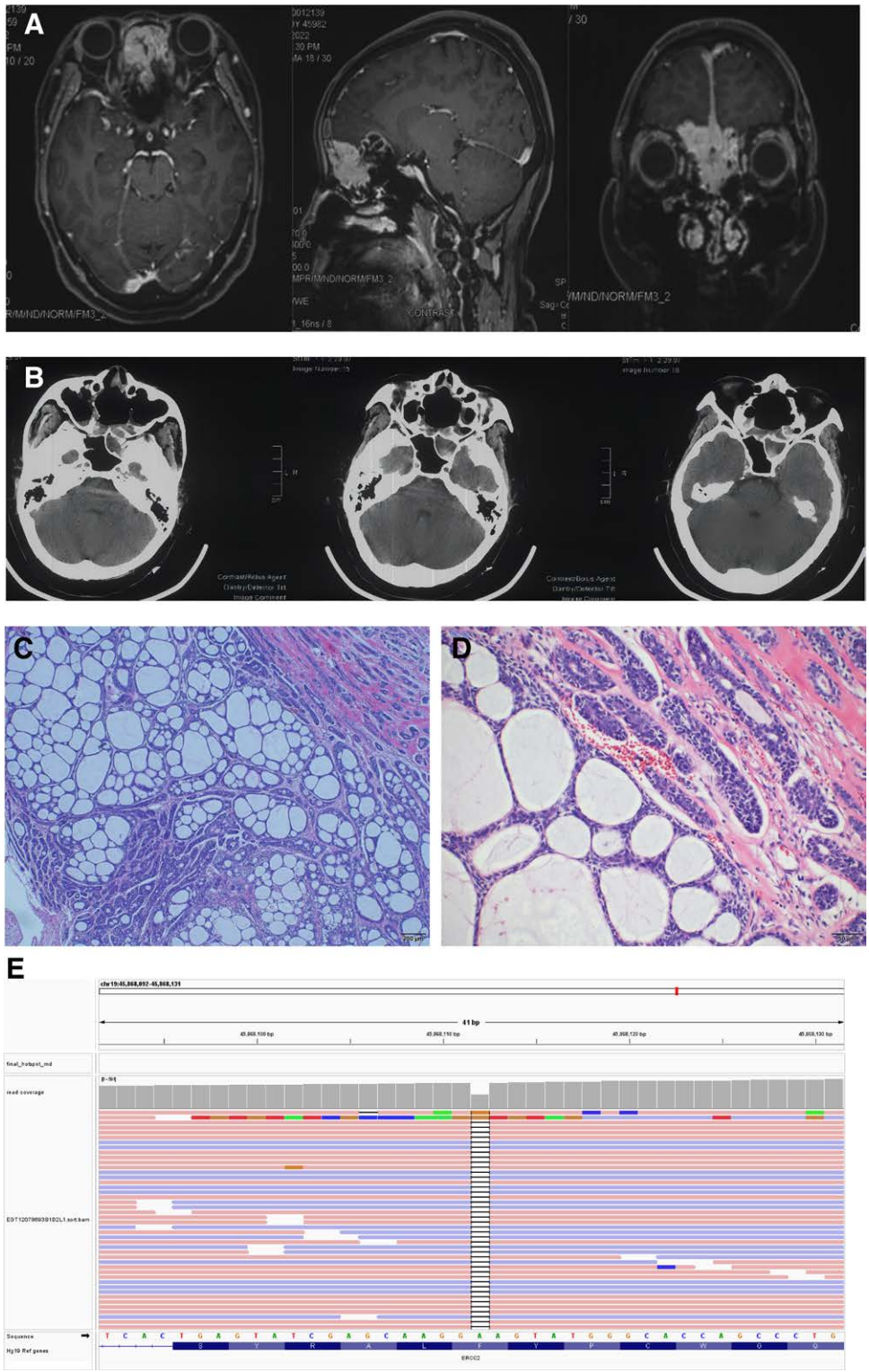

Figure 1. *ERCC2* mutation AdCC in the head and neck. MRI revealed a space-occupying lesion in the preoperative (A) and CT in the postoperative (B). Histopathologic stains (10×) (C) and (100×) (D) from skull base, nasal cavity and cranium tumor tissues suggested AdCC and next-generation sequencing revealed *ERCC2* c.578del (p. F193Sfs*55) mutation (E). AdCC = adenoid cystic carcinoma.

2. Case presentation

A 58-year-old female presented with a space-occupying lesion of the anterior cranial fossa floor during a physical examination (Fig. 1A) and sought further consultation in July 2022. Subsequently, she underwent intracranial surgery performed under general anesthesia (Fig. 1B). Postoperative immunohistochemistry revealed positive staining for tumor tissues with CK5/6, CK7, CD117, P63, S-100, CKpan, and SMA markers, and negative staining for Syn and GFAP. Additionally, the Ki-67 labeling index in tumor cells was 5%. Based on these imaging and histopathological findings, a diagnosis of AdCC was established (Fig. 1C). The patient underwent postoperative radiotherapy (RT) to the primary site approximately 2.5 months postsurgery. To date, no recurrence has been observed during follow-up.

To identify potential therapeutic targets for reducing the high recurrence rate postsurgery, the patient underwent whole exome sequencing using tumor samples and paired blood samples. Genomic profiling observed potential cancer-diver gene mutations, including a somatic mutation in *BRCA2* c.9097del (p.T3033Lfs*29) with a allelic frequency of 2.37%, and a germline mutation in *ERCC2* c.578del (p.F193Sfs*55) with a allelic frequency of 48.3%, as well as gene amplifications of *MYC* (copy number: 3.27), *CDK4* (copy number: 3.03) in tumor sample. The *ERCC2* mutation c.578del (p. F193Sfs*55) was identified as germline likely pathogenic variant in paired blood samples (Fig. 1D). The c.578del mutation in *ERCC2* gene occured in exon 7 and located within the Helicase ATP-binding domain. The mutations may cause a frameshift of the encoded amino acid at position 193, which may affect protein function (UniProt.org). This variant is absent from population databases, such as gnomAD, and has not been reported in publications. However, other frameshift mutations such as NM_000400.4 (*ERCC2*): c.2006_2007insA (p.Lys671fs; Fig. 1E) are documented as pathogenic in Clinvar (variation ID: 1028729) and loss-of-function variants in *ERCC2* are recognized as pathogenic. Additionally, no *MYB* or *MYBL1* fusions were detected. Our case reveals a rare molecular signature of co-occurring *ERCC2* inactivation and *BRCA2* inactivation in AdCC.

3. Discussion

AdCC is a rare, insidious, and highly recurrent head and neck malignancy, with no effective systemic therapy yet identified.[1] The carcinogenic mechanism of AdCC has been gradually elucidated, mainly involving the translocation of *MYB* family genes.[3] Although clinical study reveal no significant difference in overall survival (OS) between AdCC patients with or without *MYB* or *MYBL1* fusion,[3] genomic analysis helps to explore the connection between pathways and target genes in AdCC diagnosis and potential treatments. We report a rare case of AdCC with co-occurring germline *ERCC2* and somatic *BRCA2* mutations and mutually exclusive with *MYB* or *MYBL1* fusion.

The ERCC family contains 4 core tumor-associated genes (*ERCC2, ERCC3, ERCC4, ERCC5*) and the XPD protein encoded by *ERCC2* serves as the helicase subunit of the transcription factor IIH (TFIIH) complex, which is required for DNA damage verification.[7,8] ERCC2 functions as a regulator of the nucleotide excision repair (NER) pathway, which is responsible for repairing bulky DNA lesions induced by environmental mutagens, UV irradiation, and certain chemotherapeutic agents. Acting as an ATP-dependent 5' to 3' helicase, ERCC2 unwinds damaged DNA to facilitate access for other NER factors involved in subsequent repair.[9,10] Heterozygous germline mutations in *ERCC2* have been reported in lung adenocarcinoma,[11] dermatofibrosarcoma protuberans.[12] Our case is the first report of an *ERCC2* germline variant in AdCC, and we are not sure whether this mutation is directly related to genetic susceptibility to AdCC, which needs to be supported by more clinical and basic studies, but our case provides a comprehensive molecular characterization for *MYB* or *MYBL1* fusion-negative AdCC.

BRCA2 has a particularly significant function in homologous recombination-mediated DNA repair. The risk of *ERCC2* LOF mutations with AdCC is not clear, although some relevant cases have been reported.[5] Preclinical and clinical studies have linked *ERCC2* loss of function to cisplatin sensitivity.[9] Studies have reported that pan-cancer patients with DDR dysfunction like *BRCA1/2* or *ERCC* mutations have better OS after immune checkpoint inhibitors treatment.[13,14] For DDR-related mutations, PARP inhibitors may be effective for AdCC, but no reports have been reported so far. Therefore, we have reason to believe that *ERCC2* may be a potential therapeutic target for AdCC.

4. Conclusion

We found a novel germline *ERCC2* mutation and somatic *BRCA2* mutation in a patient with AdCC. Our findings expand the molecular landscape of rare *MYB* or *MYBL1* fusion-negative AdCC patients and provide a potential therapeutic strategy for this rare head and neck tumor.

Author contributions

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