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CASE REPORT

DEK::AFF2 fusion-associated middle ear non-keratinizing squamous cell carcinoma: A case report

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Abstract

BACKGROUND

Primary squamous cell carcinoma (SCC) of the middle ear is rare, with non-keratinizing basaloid types being exceptionally uncommon. Distinguishing these cancers, often caused by viral factors (*e.g.*, human papillomavirus or Epstein-Barr virus), or specific genetic alterations (*e.g.*, bromodomain-containing protein 4-nuclear protein in *testis fusion gene* or *Ewing sarcoma breakpoint region 1* gene fused with FLI chromosomal rearrangement), from other cranial conditions, is difficult. The recently identified DEK::AFF2 non-keratinizing SCC (NKSCC) is a novel subtype, fitting the World Health Organization classification of head and neck neoplasms. Less than 30 cases have been reported, highlighting the need for further studies.

CASE SUMMARY

A 55-year-old female patient first exhibited signs of illness over 10 years ago with persistent discomfort in the left external auditory canal, accompanied by skin irritation and bleeding. One month prior to seeking professional help, she experienced hearing loss and a sensation of obstruction in the affected ear, intermittently accompanied by ringing sounds, but no dizziness. An unusual mass was detected in the left auditory canal, confirmed through biopsy as moderately differentiated epithelial squamous cancer cells. This led to her admission to our hospital, where the final diagnosis confirmed as "NKSCC linked to a positive DEK::AFF2 fusion". The patient underwent surgical excision, followed by three cycles of local radiation therapy. Yet, metastasis to the lumbar vertebrae occurred 19 months post-treatment, followed by neck lymph node swelling detected three months after a physical examination. The patient died nine months later despite surgical removal of the metastatic lesion.

CONCLUSION

DEK::AFF2 gene fusion-associated NKSCC of the middle ear carries a grim prognosis and presents an emerging challenge.

Key Words: Carcinoma; DEK::AFF2; Fusion; Pathology; Case report

Core Tip: DEK::AFF2 non-keratinizing squamous cell carcinoma remains an understudied entity because of its rarity. This rare variant warrants increased attention and further exploration due to its potential severity and metastatic ability.

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INTRODUCTION

DEK::AFF2 fusion carcinoma is a subtype of non-keratinizing squamous cell carcinoma (NKSCC). This tumor was first described in 2019 by Yang *et al*[1]. It is an exceedingly rare and aggressive tumor. DEK::AFF2 NKSCC typically invades neighboring tissues, tends to recur, and may lead to nodal involvement or distal spread[2]. Most recorded instances have involved the head and neck regions, particularly affecting the nasopharyngeal cavities, ears, temporo-occipital areas, and eyes[2]. Histologically, it often presents with basaloid or non-keratinizing squamous features[3]. The emergence of this rare subtype highlights the need for increased awareness and further research due to its potential virulence and propensity for metastasis.

Herein, we report a case of DEK::AFF2 fusion NKSCC and discuss its clinical, pathological, and molecular features to elucidate the differential diagnosis of this rare tumor subtype.

CASE PRESENTATION

Chief complaints

A 55-year-old female patient presented with left external auditory canal pain and bloody otorrhea, symptoms she had been experiencing for over 10 years.

History of present illness

The patient reported persistent discomfort in the left external auditory canal, along with bothersome itching and bleeding from the affected area. Approximately one month before seeking professional attention, she began experiencing a decline in hearing on the affected side, accompanied by a sensation of congestion or blockage in that ear. She also reported episodic ringing sounds but no episodes of vertigo. Upon examination at our outpatient clinic, an unusual growth was observed in the left external auditory canal. A subsequent pathological examination of a sample obtained *via* needle aspiration confirmed moderately differentiated epidermal squamous cancer cells. The patient was admitted to our medical center for further surgical evaluation under the suspicion of a malignant neoplasm in the outermost part of the left ear canal.

History of past illness

The patient had no significant past medical history.

Personal and family history

No evident abnormalities were identified in the patient's personal or family history.

Physical examination

Inspection revealed a dark red mass on the anterior wall of the left external auditory canal. A minimal watery exudate covered the mass, completely occluding the canal and obstructing visual access to the deeper ear structures, including the tympanic membrane.

Laboratory examinations

No abnormalities were detected in the serum tumor markers.

Imaging examinations

Magnetic resonance enhanced scan (November 22, 2020; our hospital): The scan revealed a neoplasm with equal T1 and long T2 signals, clear boundaries, and dimensions of approximately 1.1 cm × 0.6 cm × 0.5 cm. The enhanced scan showed

contrast enhancement suspicious for osseous destruction, with closely adjacent vascular shadows observed in the anterior lower part of the left external auditory canal (Figure 1A).

FINAL DIAGNOSIS

DEK::AFF2 non-keratinizing squamous cell carcinoma (SCC).

TREATMENT

We subsequently performed surgical excision of the neoplasm *via* mastoidectomy and sent the specimens for pathological analysis (Figure 1B). Following the surgery, the patient underwent three cycles of adjuvant local radiotherapy. The postoperative tumor bed received a total of 60 Gy, delivered in 30 fractions. Additionally, the preauricular and postauricular parotid lymphatic drainage region was irradiated with 56 Gy in 30 fractions.

FURTHER DIAGNOSTIC WORK-UP

Postoperative pathological examination

The excised tumor was grayish-red, measuring approximately 2.0 cm × 1.6 cm × 0.5 cm. The cross-section was white-gray and solid, displaying hemorrhagic areas and visible surrounding cartilage under microscopic examination (Figure 1B). Histological analysis showed the tumor manifested as an endophytic papillary carcinoma resembling transitional epithelium with inverted nest-like proliferation patterns (Figure 2A). The tumor featured multistratified, non-keratinized squamous epithelial cells mimicking metaplastic epithelium. The basal cells exhibited fence-like arrangements, interspersed with extensive areas of necrosis (Figure 2B). The cells within the tumor showed moderate pleomorphism, eosinophilic cytoplasm, and partly clear nuclei. Inflammatory cells, including lymphocytes, plasma cells, and neutrophils, were considerably present in both the epithelial and stromal layers (Figure 2C). Immunohistochemical tests showed diffuse strong expression of keratin proteins cytokeratin 5/6 (CK 5/6), p40, and p63 in the tumor cells, with negative results for p16 and wild-type expression of p53. The Ki-67 index ranged from 15% to 25%. Tests for nuclear protein in the testis (NUT) were negative, whereas expressions of SMARCB1 (INI-1) and SMARCA4 (BRG-1) were detected. AFF2 staining showed diffuse nuclear positivity (Figure 3A). Additional immunohistochemical staining for programmed death-ligand 1 (PD-L1) revealed that approximately 40% of the tumor cells were positive (Figure 3B).

Preliminary pathological diagnosis

Non-keratinizing SCC.

Genetic testing

A retrospective analysis using reverse transcription polymerase chain reaction (RT-PCR) was negative for human papillomavirus (HPV). In situ hybridization for Epstein-Barr virus (EBV) encoded RNA also yielded negative results. Fluorescence in situ hybridization (FISH) showed disruption in the *DEK* gene structure (Figure 3C). Further molecular assays, including RT-PCR and Sanger sequencing, identified an intrachromosomal recombination event that resulted in the fusion of exon 7 of DEK with exon 5 of AFF2.

OUTCOME AND FOLLOW-UP

The follow-up period lasted 31 months, from the date of the initial operation until the patient's death. Metastasis to the lumbar vertebrae was detected 19 months after treatment (Figure 4). Three months after the removal of the metastatic lesion, an enlargement of the neck lymph nodes was observed during a physical examination. A biopsy confirmed cancer metastasis, and the patient passed away nine months later.

DISCUSSION

The newly identified DEK::AFF2 NKSCC represents a distinct type of cancer with specific genomic alterations, as recognized by the World Health Organization classification[4]. To date, only about 30 cases have been reported[5].

This cancer exhibits invasive behavior, risk of recurrence, and potential for progression to regional nodes or distant sites. It predominantly affects females aged between 18 years and 79 years and is mainly found in the head and neck, nasopharynx, ears, temporo-occipital area, eyes, and lungs. Notably, only four cases have involved the inner ear[6].

Histologically, nasopharyngeal keratoacanthomas share similar features, including: (1) Complex exophytic papillomatous structures that resemble inverted folds; (2) Basaloid/transitional epithelial cells with eosinophilic or biphasic

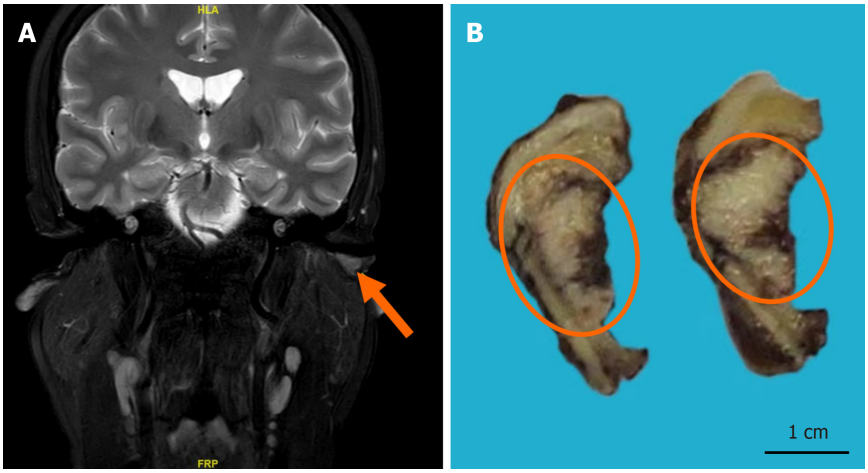

Figure 1 The magnetic resonance imaging and macroscopic view of the tumor. A: magnetic resonance enhanced scan of the inner ear canal showing a space-occupying lesion in the left external auditory canal (orange arrow); B: Macroscopic view of the tumor (orange circle).

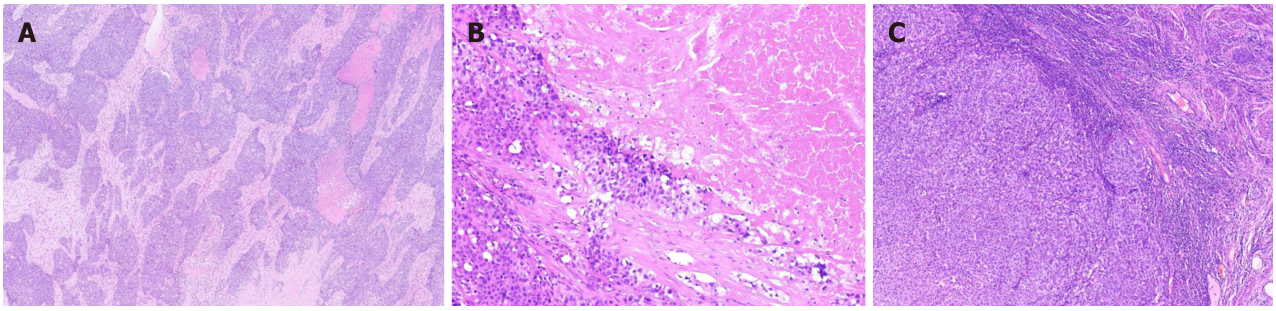

Figure 2 Histological examination of the tumor. A: Histological analysis showed the tumor manifested as an endophytic papillary carcinoma resembling transitional epithelium with inverted nest-like proliferation patterns; B: The basal cells exhibited fence-like arrangements, interspersed with extensive areas of necrosis; C: Inflammatory cells, including lymphocytes, plasma cells, and neutrophils, were considerably present in both the epithelial and stromal layers.

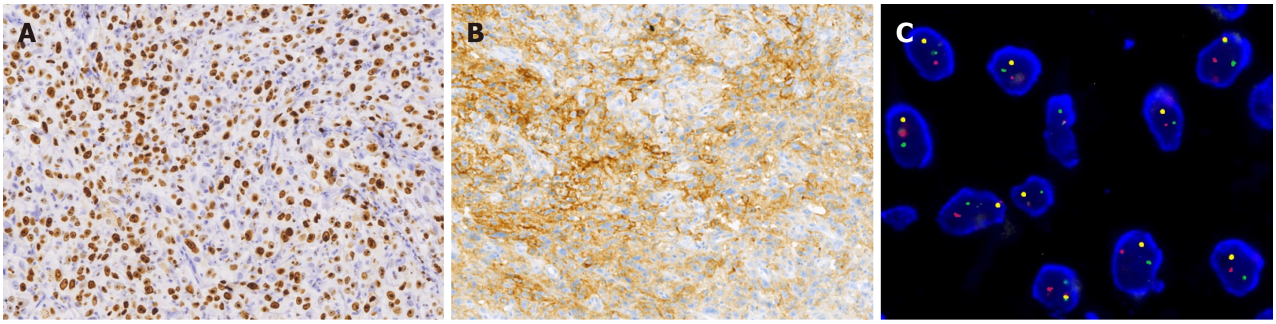

Figure 3 Immunohistochemical staining and fluorescence in situ hybridization testing of the tumor. A: Immunohistochemical staining showing tumor cells positive for AFF2 (EnVision method, medium magnification); B: Immunohistochemical staining showing tumor cells positive for programmed death-ligand 1 (EnVision method, medium magnification); C Fluorescence in situ hybridization testing revealing disruption within the *DEK* gene structure.

cytoplasm; (3) Non-keratinization or focal keratinization; (4) Uniform round to oval nuclei; and (5) Abundant inflammatory cellular infiltrates, especially neutrophils within the epithelium and stroma, and thin fibrovascular cores forming exophytic projections where interstitial connective tissue may gather. Epithelial cells often display spongiosis and loss of cohesion, leading to pseudopapillary formation[3]. Nuclear chromatin varies from fine to vacuolated in the nucleolus, with low mitotic activity and rare necrosis. Some cases also exhibit special morphological features, such as clear cell transformation, glandular cavities secreting mucoid substances, and intracellular alterations. Kuo *et al*[7] reported seven instances of deceptively benign DEK::AFF2 nasal sinus SCCs that lacked distinct stromal invasion or a marked desmoplastic response upon initial examination but eventually progressed locally, spread to regional nodes, underwent histological grade elevation, and caused extensive local destruction, leading to patient death over time. This tumor type not only closely resembles high-grade basaloid carcinoma but also shares features with benign papillomas and low-grade Schneiderian papillary adenocarcinomas, making molecular pathology testing crucial to avoid misdiagnosis. The pa-

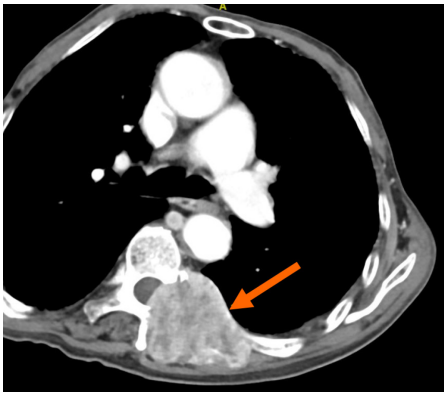

Figure 4 Computed tomography scan of metastatic lesions. The computed tomography scan shows thoracic vertebral metastatic lesions (orange arrow).

tient's specimen showed typical papillomatous architecture without significant cytomorphological aberrations or stromal penetration. The lesion displayed combined exophytic and endophytic growth patterns with light to moderate nuclear pleomorphism confined largely to small foci, rather than the diffuse invasiveness characteristic of typical SCC. These factors likely contribute to the repeated sampling and diagnostic challenges encountered.

Immunophenotypically, the tumor cells diffusely expressed CK 5/6, p63, and p40. NUT was negative, whereas expression of SMARCB1 (INI-1) and SMARCA4 (BRG-1) remained intact[6]. The *DEK::AFF2* gene fusion is characteristic of this malignancy[8]. Therefore, immunohistochemical detection using an AFF2 c-terminal antibody serves as a sensitive and distinctive marker for diagnosing DEK::AFF2 carcinoma[9]. Our case was validated using this method to confirm its specificity. Additionally, DEK was verified by rearrangement or fusion with AFF2 using FISH analysis. RT-PCR followed by Sanger sequencing further clarified the exact location of the fused *DEK::AFF2* gene.

The prognosis for individuals diagnosed with DEK::AFF2 fusion NKSCC is unfavorable, as approximately 20% develop regional nodal involvement and 17% experience distal spread, often affecting the lungs, skeleton, and central nervous system[2]. No standard management protocols exist due to the rarity of documented cases. The primary mode of intervention typically involves surgical excision, followed by adjuvant radiation, chemotherapy, or immunotherapies[8]. This patient received traditional standard care methods, including surgical resection and radiation therapy, but not immunotherapy. At the initial stages of diagnosis, the small size of the tumor mass and unique nature of the fused gene did not attract adequate attention. However, subsequent testing involving PD-L1 immunohistochemistry revealed promising indications that tumor cells may respond favorably to programmed cell death 1/PD-L1 immunotherapy[10]. These findings suggest that individuals with this rare condition could potentially benefit from this form of treatment[11]. Kuo *et al*[7] reported encouraging responses to the immune checkpoint inhibitor pembrolizumab in treating an individual harboring the DEK::AFF2 fusion NKSCC. Nonetheless, a few patients succumbed to disease relapse within 29 months post-immunotherapy, underscoring the necessity for further case accrual to gauge the efficacy of immunomodulatory strategies for this condition[12].

CONCLUSION

DEK::AFF2 NKSCC represents a significant diagnostic challenge. In our routine diagnostic work, if we encounter complex papillary non-keratinized SCCs in the head and neck area (including the nasal cavity, paranasal sinuses, ears, and cranial base), even after ruling out HPV, EBV, SMRCB1/SMARCA4, or NUT-related malignancies, the possibility of DEK::AFF2 fusion NKSCC should be considered.

FOOTNOTES

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