OPEN ACCESS – CASE REPORT

DEK::AFF2 Squamous Cell Carcinoma is a Deceptive Mimic of Inverted Sinonasal Papilloma: A Case Report

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ABSTRACT

An elderly Filipino female presented with a 5-year enlarging left nasolacrimal mass initially diagnosed as Inverted Papilloma of the Lacrimal Sac. Repeat biopsy revealed a papillomatous neoplasm with thick and thin papillae, solid invaginating lobules, and anastomosing trabeculae of monomorphic squamotransitional cells, briskly infiltrated by neutrophils. Mucocytes, respiratory epithelium, and microcysts, typical of Inverting Sinonasal Papilloma, are absent. Immunohistochemistry, including a validated AFF2 IHC, confirmed the diagnosis of *DEK::AFF2* sinonasal carcinoma. Awareness of this emerging entity is essential to prevent misdiagnosis and prompt surgical management.

Key words: DEK, AFF2, squamous cell carcinoma, case report, Philippines

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INTRODUCTION

DEK::AFF2 sinonasal carcinoma is an emerging entity in the sinonasal tract and skull base classified as a subtype of Non-keratinizing Squamous Cell Carcinoma. However, it is likely an under-recognized neoplasm often misdiagnosed as a benign inverted sinonasal papilloma (ISP) due to its frequent papillomatous growth and strikingly bland monomorphic cytology.[1-5] Alternatively, due to its banal appearance, some cases of *DEK::AFF2* sinonasal carcinoma have been previously classified as "low-grade papillary Schneiderian carcinoma."[2-6] A subset of cases may also display overt carcinomatous features similar to non-keratinizing squamous cell carcinoma or adenosquamous carcinoma of the sinonasal tract and skull base.[2,3,5] The diagnosis is made upon evaluation of key histologic and immunophenotypic features followed by confirmatory molecular testing for the *DEK::AFF2* fusion or a validated immunohistochemical (IHC) assay for the AFF2 protein, as a confirmatory surrogate.[3] Increasing awareness is important as this tumor can have frequent local recurrences, occasional lymph node and distant metastases, and rare tumor-related deaths.[3,5] Here, we report the first diagnosed case of *DEK::AFF2* sinonasal carcinoma in an elderly Filipino patient.

CASE

A 76-year-old female presented with a 5-year history of an enlarging left nasolacrimal mass. The mass began at the medial aspect of the left eye, with associated tearing and discharge. Eye drops were initially prescribed but afforded no relief from symptoms. She then sought consultation from another institution, where she was diagnosed with Chronic Dacryocystitis and Nasolacrimal Duct Obstruction, and subsequently underwent laser dacryocystorhinostomy. The patient reported slight relief of symptoms. However, in the interim, there was a gradual enlargement of the mass with an increase in tearing and discharge. Two months before the consult, a biopsy was done in another institution, where she was diagnosed with papilloma of the lacrimal duct, inverted type. Antibiotics

were prescribed, but the mass continued to increase in size, now with a left nasal extension. The patient eventually sought a consultation at the outpatient department.

On physical examination, there was a 4.0 x 4.0 x 2.0 cm firm, non-tender, fixed nodular mass on the left maxilla involving the left orbit and medial canthus. There was noted tearing and crusting of the left eye. On rhinoscopy, there was a fleshy mass completely obstructing the left nasal cavity. The rest of the physical examination, family history, and previous medical history are unremarkable.

Imaging showed that the mass arose from the left lacrimal sac with extension to the pre- and post-septal cavity, abutting the medial rectus muscle. The mass also extends to the inferomedial aspect of the globe, left frontal sinus, left anterior ethmoid sinus, and left nasal cavity, indenting the turbinates, and occupying the left nasolacrimal sac and duct. Mild septal deviation is seen (Figure 1A). No intracranial extension was noted. The right frontal, ethmoid, and sphenoid sinuses, as well as the right nasal cavity, are uninvolved. A repeat biopsy was done and sent for histopathologic examination.

The tissue sample consists of several tan-brown fleshy fragments with an aggregate dimension of 3.5 cm. Histologic examination shows a papillomatous neoplasm forming thin and thick papillae, solid endophytic lobules, and anastomosing trabeculae of epithelial tumor cells (Figure 1B). The endophytic lobules comprise a solid proliferation of squamotransitional cells reminiscent of inverting sinonasal papilloma (Figure 1C). However, in contrast to inverting sinonasal papilloma, the neoplastic epithelium does not contain mucocytes, intermediate or respiratory-type epithelial cells, and microcysts that contain microabscesses. Instead, the polygonal tumor cells display striking monomorphism, ovoid vesicular nuclei, conspicuous nucleoli, and ample eosinophilic cytoplasm. An accompanying brisk peritumoral and intratumoral neutrophilic infiltrate is seen (Figure 1D). Due to the aforementioned histologic findings, immunohistochemical work-up using Pancytokeratin (AE1/AE3), p63, NUT, INI-1, and AFF2 for the C-terminus were performed. The tumor showed strong and diffuse expression of pancytokeratin and p63 (Figure 1E), confirming an epithelial neoplasm with squamous differentiation, was negative for NUT *(image not included)*, ruling out a NUT carcinoma, and had retained expression of INI-1 *(image not included)*, excluding a SMARCB1-deficient sinonasal carcinoma. The tumor showed a strong diffuse nuclear expression of AFF2 in all tumor cells (Figure 1F), confirming the diagnosis of *DEK::AFF2* sinonasal carcinoma. The patient underwent complete resection of the tumor, including the orbital contents.

DISCUSSION

Epidemiology/Incidence

Sinonasal carcinomas are rare (1/100,000 population) and aggressive tumors that represent 3-5% of all head and neck cancers. Investigation of publicly available RNA data sets of sinonasal papillomas and squamous cell carcinomas and review of recurrent sinonasal papillomas over a two-decade period have suggested *DEK::AFF2* sinonasal carcinoma to occur in 4.7-10.7% of cases. A total of 49 cases has been published to date.[1-10] This is the first reported case of *DEK::AFF2* sinonasal carcinoma in the Philippines.

Clinicopathologic features, presentation, and anatomic involvement

DEK::AFF2 sinonasal carcinoma most frequently involves the nasal cavity. This is followed in decreasing order of frequency by the nasopharynx, skull base, paranasal sinuses, middle ear, orbit, temporal bone, and rarely, by the lacrimal sac, similar to the present case.[3,5] Interestingly, a case of *DEK::AFF2*-rearranged carcinoma has been reported in the lung with broncho-centric growth and co-expression of p40 and TTF-1, suggesting a potential origin from the basal cells of the respiratory epithelium.[7]

Morphologic features, differential diagnosis, and ancillary work-up

The histologic features of *DEK::AFF2* sinonasal carcinoma usually fit into three distinct morphologic patterns, which may guide pathologists to its recognition. The Low-grade Papillary Schneiderian Carcinoma subtype is the most common. From its namesake, prior cases with this morphologic pattern were previously classified as "Low-grade Papillary Schneiderian Carcinomas" but were later found to harbor the defining *DEK::AFF2* fusion, resulting in their reclassification.[2,6] In this subtype, the neoplastic epithelium forms endophytic lobules usually with rounded non-infiltrative contours and anastomosing trabeculae, resembling ISP, its closest differential. In contrast to ISP, the tumor usually displays a greater architectural complexity, with back-to-back invaginating lobules and trabeculae forming a maze-like or labyrinthine pattern. Furthermore, the cells are strikingly monomorphic and bland, without the usual admixture of squamous, mucocytes, and respiratory-type cells in the epithelium and abscess-containing microcysts, which are distinguishing features of ISP. Likewise, these cell components are required to be at least focally present in ISP with dysplasia or carcinoma-ex ISP. Conspicuous central acantholytic change in the lobules confers a dilapidated appearance, pseudopapillary pattern, or areas reminiscent of stellate reticulum, which could be mistaken for ameloblastic epithelium. Stromal neutrophilic infiltrates surround the lobules or infiltrate between tumor cells.[2,3,6] Less commonly, *DEK::AFF2* sinonasal carcinoma may display an infiltrative pattern with varying but often limited squamous and/or glandular differentiation, corresponding to the non-keratinizing squamous cell carcinoma and adenosquamous carcinoma morphologic subtypes. When encountering these 2 morphologic subtypes, a wide range of differential diagnoses is considered. Briefly, cases of non-keratinizing squamous cell carcinoma subtype should be distinguished from 1) Virus-related (EBV or HPV) carcinomas; 2) Squamous cell carcinoma arising from ISP with an underlying EGFR-mutation; 3) poorly-differentiated malignant neoplasms with squamous phenotype to include NUT carcinoma, SWI/SNF-related carcinoma, and adamantinoma-like ewing sarcoma; and 4) Carcinogen-driven squamous cell carcinomas. Cases with adenosquamous carcinoma should be distinguished from HPV-multiphenotypic sinonasal carcinoma, adenosquamous carcinoma, and from mucoepidermoid carcinoma. Thus, work-up to variably consist of p40, p16,

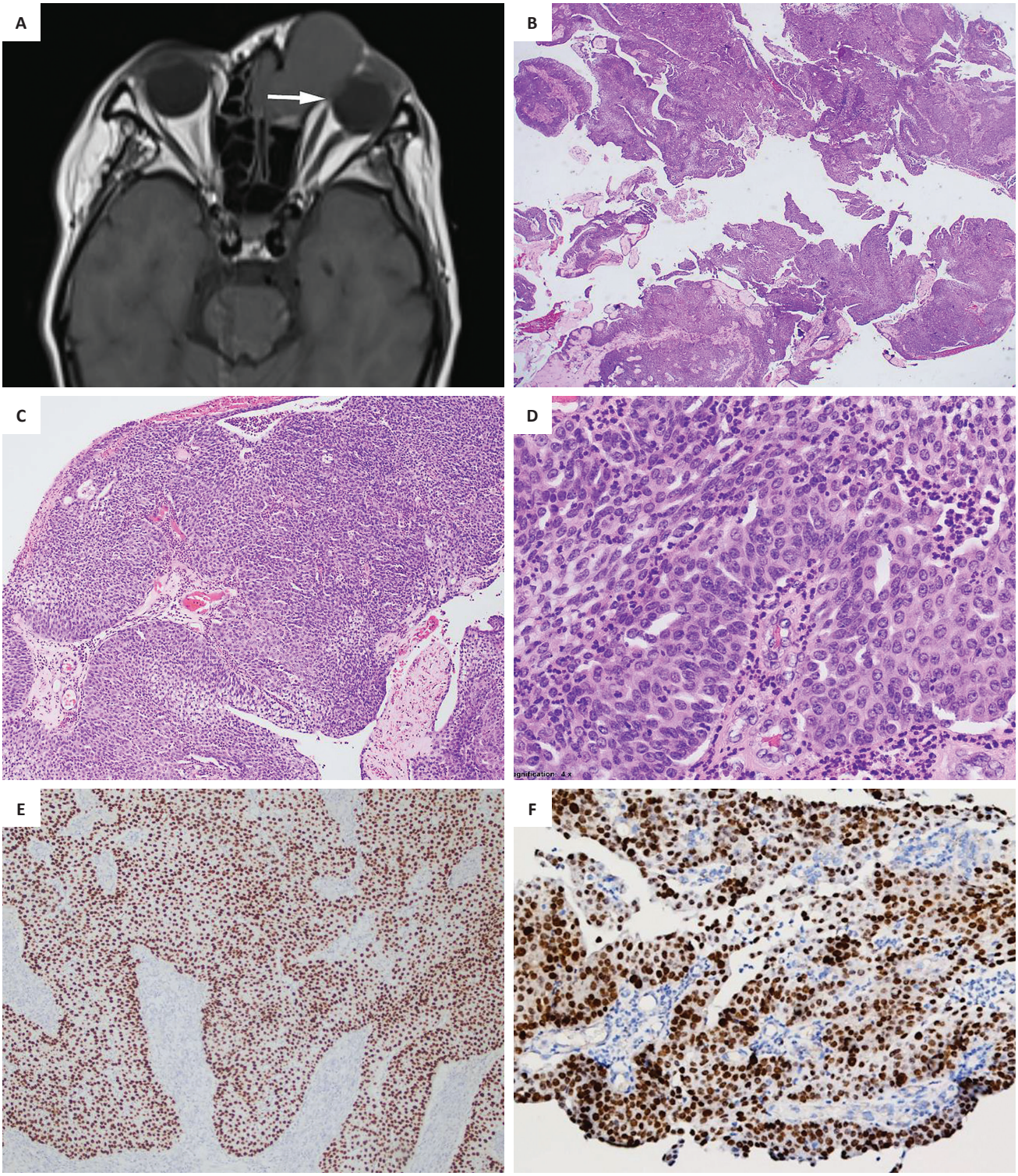

Figure 1. ***Imaging and histopathologic findings of the case.*** **(A)** Imaging shows the tumor in the ethmoid sinus and left nasal cavity. It abuts the medial rectus muscle and displaces the left globe *(white arrow)*. **(B)** Tumor fragments consist of papillae, solid endophytic lobules, and anastomosing thick trabeculae of tumor cells (H&E 40x). **(C)** Solid endophytic lobules resemble those of inverting sinonasal papilloma but with greater cell crowding and solid growth (H&E 100x). **(D)** Squamo-transitional tumor cells are monomorphic with ovoid vesicular nuclei and ample eosinophilic cytoplasm. Mucocytes, respiratory epithelium, and microcysts typical of ISP are not observed. Neutrophils surround the tumor cell clusters or infiltrate between tumor cells (H&E 400x). **(E)** Tumor shows nuclear expression of p63 (IHC 200x). **(F)** Tumor shows strong diffuse nuclear expression of AFF2 in all cells (IHC 200x).

NUT, INI-1, BRG1, CD99, and NKX2.2 IHCs, EBERish and HPVish, and/or molecular testing for *MAML2* gene rearrangement, will select cases requiring further *DEK::AFF2* fusion confirmatory testing.[3,8,9]

Molecular testing and AFF2 IHC

The diagnosis of *DEK::AFF2* carcinoma is based on the presence of the defining *DEK::AFF2* gene fusion. The *DEK::AFF2* fusion has been identified using whole-genome sequencing,[10] whole transcriptome sequencing,[2] targeted RNA next-generation sequencing (NGS),[1,11,12] and/or fluorescent in situ hybridization (FISH) using *DEK* dual fusion or break-apart probes.[2,6,10,13,14] Furthermore, recognition of the breakpoints and fusion variants has led to the development of specific primers to identify the *DEK::AFF2* fusion via reverse transcription polymerase chain reaction (RT-PCR).[6] More recently, studies on the differential AFF2 protein expression in fusion-positive tumors have led to the development of an immunohistochemical assay targeting the C-terminus peptide of the AFF2 protein.[2] An adequately validated AFF2 IHC has demonstrated excellent sensitivity, specificity, positive predictive value, and negative predictive value as a surrogate marker for the *DEK::AFF2* fusion when at least 30% of tumor cells are observed to display moderate to strong nuclear expression.[2,5,14,15] Thus, in resource-limited settings, RT-PCR or a rigorously validated AFF2 IHC, combined with morphologic evaluation and an appropriate immunohistochemical panel to exclude other differentials, is an effective method to confirm the diagnosis of *DEK::AFF2* sinonasal carcinoma.

Prognosis/clinical behavior

DEK::AFF2 sinonasal carcinoma shows frequent local recurrences or progression (50-55.5%) with occasional lymph node (25.0-29.6%) and distant (17-25.9%) metastases. Tumor-related deaths are found to range from 5.9% to 25%, depending on the reported case series, with variable median follow-up (7-18 months).[3,5]

CONCLUSION

DEK::AFF2 sinonasal carcinoma is an under-recognized malignant neoplasm. Frequently, it shows papillomatous growth with banal and strikingly monomorphic tumor cells, easily misconstrued as an inverting sinonasal papilloma. In these cases, accurate diagnosis is facilitated by identifying architectural complexity, strikingly monomorphic tumor cells, absence of the typical cellular components of inverting sinonasal papilloma (mucocytes, respiratory-type epithelial cells, and microcysts), and peritumoral neutrophilic infiltrates. An appropriate IHC panel and molecular testing for the *DEK::AFF2* fusion or an AFF2 IHC targeting the C-terminus as a surrogate will confirm the diagnosis. Awareness of this emerging entity to distinguish from ISP is clinically relevant to prevent delay in surgical management, as it has been shown to behave aggressively with frequent local recurrence, occasional metastasis, and rare tumor-related deaths.

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STATEMENT OF AUTHORSHIP

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AUTHOR DISCLOSURE

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