

DEK::AFF2 fusion positive carcinoma, a potentially misdiagnosed entity: overview of histology and diagnostic clues

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Abstract

We report a case of an 88-year-old male with a large nasal lesion thought to be an inverted papilloma clinically and on imaging, but subsequently diagnosed histologically as a carcinoma, specifically, a non-keratinizing squamous cell carcinoma with the distinct DEK - AFF2 fusion. This variant of carcinoma in the head and neck is an emerging entity thought to have a distinct morphology, that should prompt molecular studies. Overlapping histological features with benign papillomatous lesions emphasizes the need for identification of this entity, as they have been associated with an aggressive clinical course including relapse and distant metastases. In addition, identification of the specific fusion may potentially add to the therapeutic armamentarium.

Keywords DEK-AFF2 fusion; inverted sinonasal papilloma; non-keratinizing squamous cell carcinoma; sinonasal carcinoma

Case report

After falling, an 88-year-old male attended A&E with epistaxis and nasal blockage. The ENT clinic assessment suspected an inverted papilloma (IP) and imaging was requested. Consistent with the

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clinical impression, imaging found a heterogeneous enhancing mass effacing the entire right nasal cavity from the piriform aperture to the choana, extending into the postnasal space and causing opacification of the right maxillary sinus (Figure 1). Following standard practice, endoscopic excision of the large polypoid lesion without a biopsy was completed. Histology revealed an ulcerated polypoid lesion covered partially by non-keratinizing stratified squamous epithelium and fibrinopurulent slough. The underlying stroma was largely effaced by a proliferative epithelial lesion organized as complex anastomosing broad bands of epithelium diffusely permeated by neutrophils, often forming microabscesses. The epithelial proliferation featured prominent peripheral cell palisading in several parts, and foci of basaloid morphology and clear cell change (Figures 2–4). Marked cytological atypia and atypical mitotic figures were rare. A desmoplastic stromal response and moderate host chronic inflammatory cell infiltrate was elicited. On immunohistochemistry, the neoplastic cells expressed p63, CAM5.2 & p53 (strong diffuse), CK5, CK7, 34BE12 & p40 (heterogeneous) and p16 (heterogeneous). CK14, CK20, SOX-10, S100, GATA3, PAX-8, SALL-4, OCT3/4, EBER and HPV genotyping were negative (Figures 5 and 6). Based on the histology and immunohistochemistry, the diagnosis was a non-keratinizing squamous cell carcinoma. RNA based next generation sequencing (NGS) identified DEK::AFF2 fusion, resulting in a final diagnosis of DEK::AFF2 squamous cell carcinoma.

The unexpected diagnosis prompted additional clinical and imaging investigations, which confirmed absence of residual disease and distant metastasis. Further management proposals included adjuvant radiotherapy and clinical follow up.

Discussion

Non keratinizing squamous cell carcinomas (NKSCC) of the head and neck comprise a heterogeneous group featuring variable aetiology and underlying molecular alterations. Human papilloma virus (HPV), most commonly type 16, drives a subset. In-frame DEK::AFF2 fusion in NKSCC is a recent discovery. It is a tumour type-specific fusion generated by chromosomal translocations in HPV negative NKSCC. Classified as an emerging entity by the WHO, it is reportedly found in more than half of HPV negative NKSCCs.¹ The first reported case, a metastatic skull base NKSCC, showed remarkable response to immune checkpoint inhibitors (ICI) despite low tumour mutational burden and lack of PD-L1 expression. Further exploratory work found a DEK::AFF2 neoantigen-specific T-cell response.²

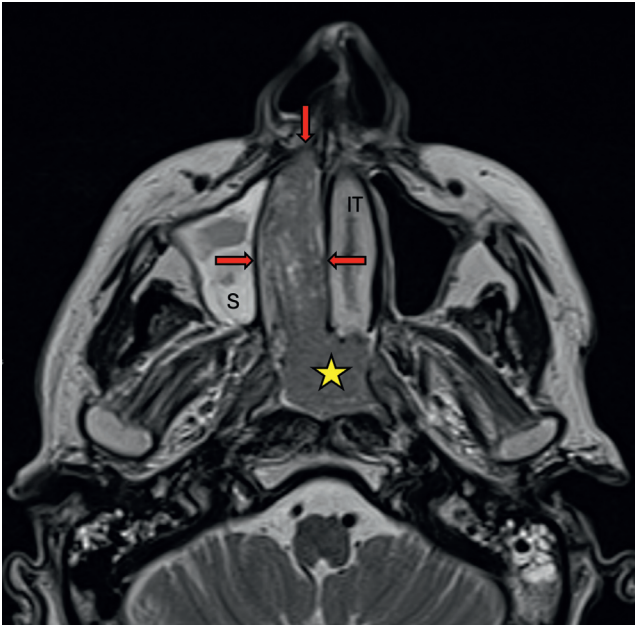


Figure 1 MRI of squamous cell carcinoma in the right nasal cavity. This T2-weighted axial sequence shows an intermediate signal mass (red arrows) filling the length of the right nasal cavity with a bulky component within the nasopharynx (yellow star). The lesion abuts but does not macroscopically infiltrate the medial maxillary antral wall laterally, the nasal septum medially, and the nasopharyngeal mucosa posteriorly. It is distinct from the normal contralateral inferior turbinate (IT) and retained maxillary antral secretions (S), both of which demonstrate high signal.

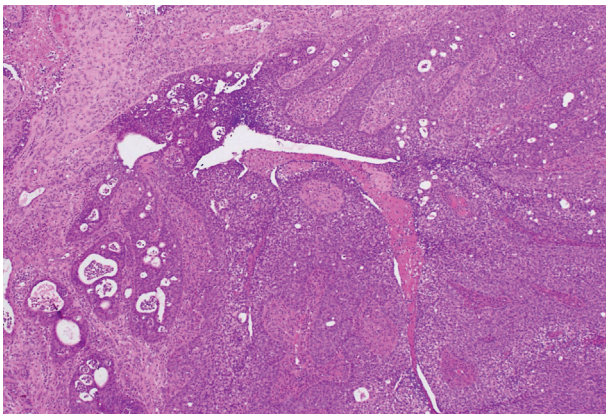


Figure 2 Histology (H&E) section showing complex anastomosing bands of squamous epithelium with neutrophil exocytosis and frequent neutrophil micro-abscesses (x100 magnification).

Case series have highlighted the potentially distinct morphological and clinical characteristics of head and neck tumours with this fusion.²⁻⁵ Common histological features are an exophytic and endophytic, often papillary growth pattern, complex anastomosing broad lobules or trabeculae, cellular monotony, acantholytic change, dense neutrophilic infiltrate and peripheral palisading. Additional features noted are basaloid morphology, glandular differentiation, cellular and keratin whorls, clear cells and ciliated surface.² Differential diagnoses therefore include low-grade sinonasal papilloma, adenosquamous carcinoma and non-keratinizing carcinomas of various types. Histological diagnosis requires distinction from high risk HPV and Epstein Barr virus (EBV) driven non-keratinizing carcinomas, carcinomas arising

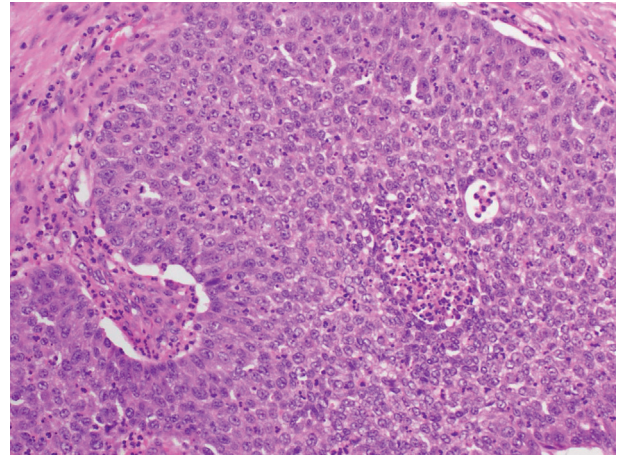


Figure 3 Histology (H&E) section showing monotonous cellular morphology, a diffuse neutrophil infiltrate and occasional neutrophil abscesses (x300 magnification).

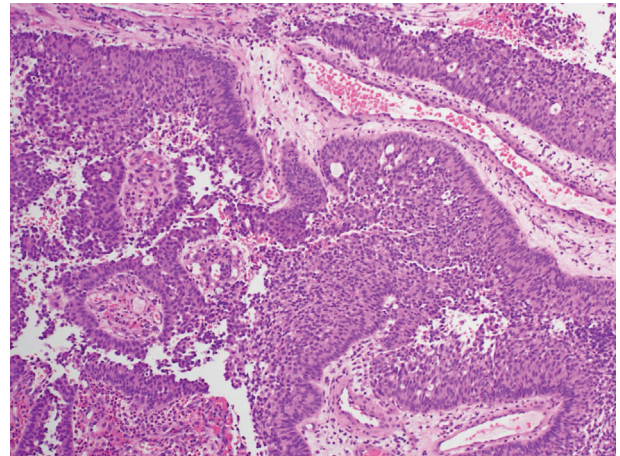


Figure 4 Histology (H&E) section showing irregular broad anastomosing bands of tumour with acantholysis and prominent peripheral palisading of cells (x200 magnification).

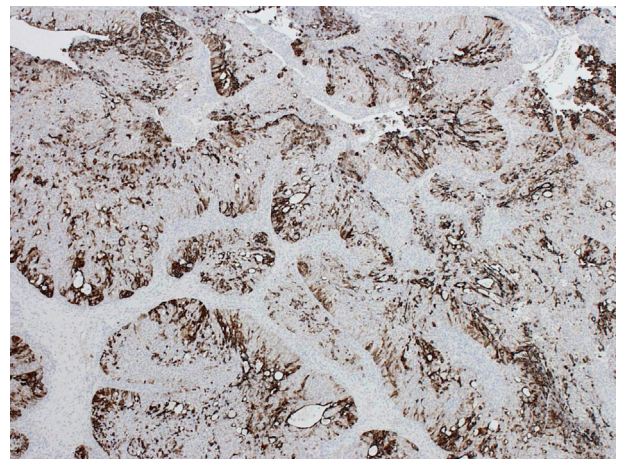


Figure 5 Immunohistochemistry for CK5 showing heterogeneous expression in neoplastic cells (x100 magnification).

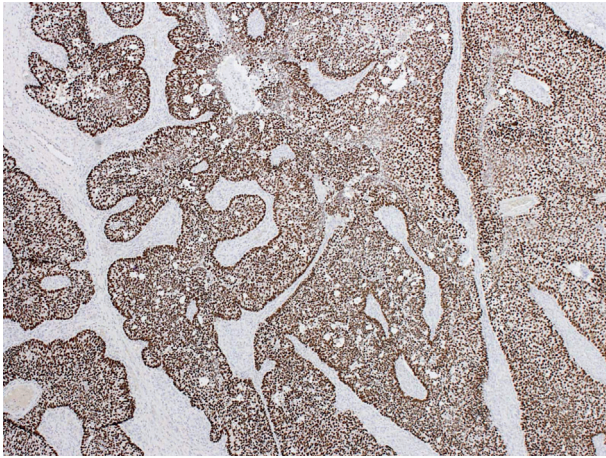


Figure 6 Immunohistochemistry for p63 showing diffuse expression in nearly all neoplastic cells (x100 magnification).

from oncocytic and inverted papilloma; NUT, SWI/SNF deficient and undifferentiated carcinoma to adamantinoma-like Ewing's sarcoma. In reviews, around 50% had previously been diagnosed as either benign or malignant Schneiderian papilloma.

Molecularly defined sinonasal malignancies are increasingly being discovered. However, identification often relies on next generation sequencing (NGS), fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) testing, rather than immunohistochemistry, and delays diagnosis through needing referral to genomic hubs.⁶ The ever-growing spectrum of genetic alteration specific immunohistochemistry could potentially aid rapid diagnosis. Immunohistochemistry for AFF2 protein is specific and could locally distinguish DEK::AFF2 fusion driven carcinomas from differential diagnoses.⁷

Reported cases displayed aggressive clinical course including relapse and occasional lymph node and distant metastases.^{2–5} Most patients received surgery with or without chemotherapy and radiotherapy and the literature lacks adequate evidence on ICI response. However, awareness of the entity and subsequent accurate diagnosis may help develop effective targeted therapeutic protocol, with resultant improved outcomes.

Conclusion

This is a case report of a sinonasal polyp suspected to be an IP, but established histologically as malignant, specifically a DEK::AFF2 squamous cell carcinoma. Recognizing key morphological features alongside ancillary testing is pivotal and should trigger molecular testing for identification of fusion-driven carcinomas. Without easy access to NGS and fusion protein-specific immunohistochemistry, there is the potential for under-reporting of this entity. The limited literature available suggests a poorer prognosis and an aggressive disease course. Therefore, the clinical need for identification of this tumour is important, not just

for its recognition from benign sinonasal papilloma and differential management as a carcinoma, but also the potential for future access to targeted therapy. ◆

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Practice points

- Biopsy specimens of suspected sinonasal papillomas should be entirely processed for histological examination
- Differentiation from benign sinonasal papilloma is crucial and histology displaying an exo- or endophytic growth pattern with complex broad to bulbous trabeculae, in addition to monotonous cytomorphology, instead of the smooth surfaced rounded inverted growth pattern of benign inverted papilloma, should prompt molecular diagnostics for definitive diagnosis
- Differentiation from other subtypes of sinonasal carcinoma will require utilization of a combination of immunohistochemistry and molecular diagnostics
- Going forward, the utilization of routine NGS testing on sinonasal carcinomas may be recommended for identification of novel fusion driven sinonasal malignancies with therapeutic implications

Self-assessment questions

1. What type of molecular alteration is seen in DEK::AFF2 squamous cell carcinoma?

- A. Gene amplification
- B. Fusion
- C. Substitution
- D. Deletion
- E. Exon skipping

Answer: B

2. Which of the following tests would be both negative in DEK-AFF2 squamous cell carcinoma?

- A. HPV genotyping and EBER
- B. P16 and EBER
- C. CK20 and CK7
- D. HPV genotyping and P63
- E. P40 and P16

Answer: A

3. What architectural pattern has been most described in DEK::AFF2 squamous cell carcinoma?

- A. Solid sheets with necrosis
- B. Back to back small glands or acini
- C. Irregular nests, cords or single neoplastic cells in desmoplastic stroma
- D. Nests, trabecular or insular pattern
- E. Complex exophytic and endophytic growth with anastomosing structures

Answer: E