HPV Related Multiphenotypic Sinonasal Carcinoma: An Emerging Pathologic Entity

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ABSTRACT: Human papillomavirus-related multiphenotypic sinonasal carcinoma (HMSC) is a recently recognised, uncommon malignancy of the sinonasal tract characterised by a distinctive biphasic morphology and consistent association with high-risk HPV types, most often HPV-33. Although histologically high-grade, HMSC paradoxically demonstrates a relatively indolent clinical course, making accurate diagnosis crucial to avoid overtreatment. We report the case of a 42-year-old female who presented with unilateral epiphora and a painful, firm left-sided facial swelling of five months' duration. This case reinforces the importance of recognising the characteristic morphology and immunophenotype of HMSC. Increased awareness of this emerging entity is essential to ensure appropriate diagnostic classification and optimal clinical management.

KEYWORDS: Human papillomavirus-related multiphenotypic sinonasal carcinoma, Human papillomavirus, Paranasal Sinus, Immunophenotype

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INTRODUCTION: Less than 1% of all cancers and roughly 5% of head and neck cancers are sinonasal carcinomas. The majority of squamous cell carcinomas of the oropharynx are known to be caused by human papillomavirus (HPV).[1]Although the sinonasal tract is a second anatomic favourite for HPV-related head and neck carcinomas, it is yet unknown how these carcinomas behave. HPV-related multiphenotypic sinonasal carcinoma (HMSC) is a rare sinonasal neoplasm characterised by a biphasic appearance with myoepithelial and ductal cells, often high-grade histologic features, frequent surface squamous atypia, and consistent association with uncommon high-risk HPV types.[2]The majority of HMSCs affect the nasal cavity (89%) with a turbinate predilection and with or without concurrent paranasal sinus involvement.Most patients present with obstruction and epistaxis and are nearly always localised to the sinonasal tract at presentation.[1] HMSC typically affect adults (mean age 54 years) with a slight female predominance. HPV testing of squamous cell carcinomas exhibits a 20-30% of sinonasal cancers harbouringhigh-risk HPV.[3]Owing to the bewildering variety of cellular components (hence the term multiphenotypic), which could be mistaken for squamous cell carcinoma or salivary gland adenoid cystic carcinoma by an unsuspecting pathologist and clinician, we would like to present one such case diagnosed in a 42-year-old female who presented with unilateral epiphora and a painful, firm left-sided facial swelling of five months' duration.

CASE REPORT: Our patient presented with complaints of unilateral epiphora and painful left-sided hard, tender, and non-fluctuant facial swelling for 5 months, extending from the dorsum of the nose to the medial canthus and glabella. The contrast-enhanced computed tomography (CECT) nose/paranasal sinus showed marked osteolysis of the left ethmoid bone with associated new bone formation and moderately enhancing soft tissue mass in the left frontal sinus, suggesting a malignant aetiology. (Figure-1)

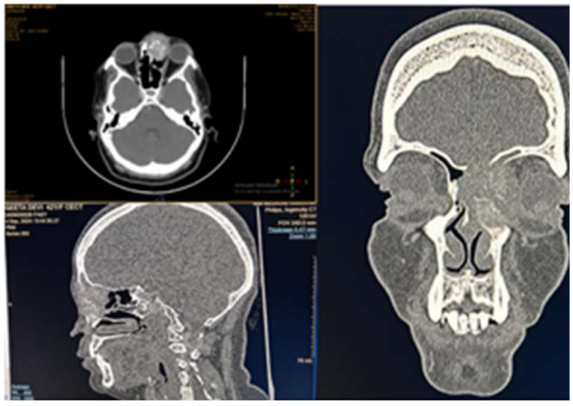

Fig 1: CECT nose/paranasal sinus showed marked osteolysis of left ethmoid bone with associated new bone formation and moderately enhancing soft tissue mass in left frontal sinus, suggesting a malignant etiology.

Histopathological examination revealed a malignant epithelial tumour with tubules comprising bilayered inner epithelium and an abluminal myoepithelial/basal layer. Multiple nests of small basaloid cells with increased N:C ratio and coarse chromatin were also evident, along with cortical bone infiltration and focal neo-woven bone formation. (Figure-2)

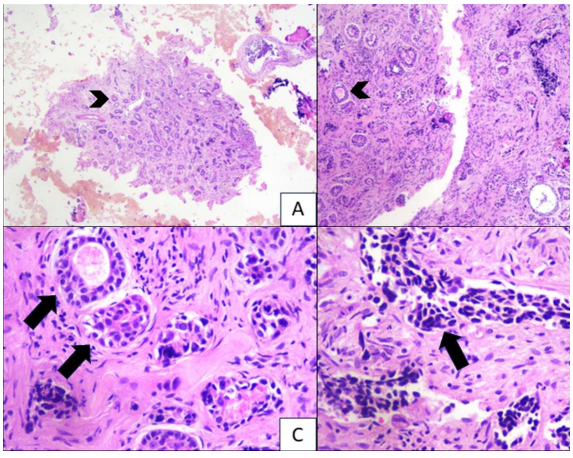

Fig 2: Histopathological examination revealed a malignant epithelial tumor with the presence of tubules (arrowheads) comprising of bilayered inner epithelium and an abluminal myoepithelial/ basal layer. (A, x40; B, x100, Hematoxylin & Eosin) Multiple nests of small basaloid cells (arrows) with increased N:C ratio and coarse chromatin were also evident, along with cortical bone infiltration and focal neo-woven bone formation. (C, x400; D, x400, Hematoxylin & Eosin)

A representative immunohistochemistry panel with CK7 positivity in epithelial cells and small basaloid cells, p63 and S100 positivity in abluminal cells lining tubules while being negative in basaloid cells, strong nuclear and cytoplasmic p16 in epithelial cell lining tubules and focal small basaloid cells, retained expression of INI-1, along with negative synaptophysin, chromogranin, INSM1, HMB45 and SATB2 has been shown in Figure-3. In situ hybridisation for high-risk HPV (especially serotype 33) was recommended for confirmation of diagnosis. The patient was also advisedof surgical excision; however,she declined the same and is currently on palliative care.

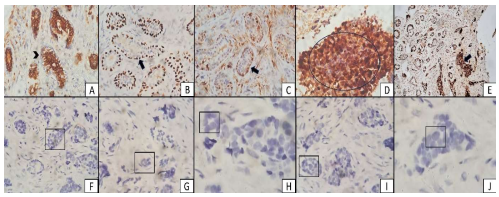

Fig 3: IHC showed (A) positive CK7 in epithelial cells & small basaloid cells, (x100,arrowhead); (B-C) p63 & S100 positivity in abluminal cells lining tubules while being negative in basaloid cells, (x100,arrow); (D) strong nuclear & cytoplasmic p16 in epithelial cell lining tubules & focal small basaloid cells, (x400,circle) (E) retained INI-1 (x40,arrow) along with negative (F) synaptophysin (x100); (G) chromogranin (x100); (H) INSM1 (x400) (I) HMB45 (x100); & (J) SATB2 (x400) (square).

DISCUSSION: The many lines of cellular differentiation that are frequently found in a single tumour are referred to be 'multiphenotypic'.[3]The proliferation of basaloid cells as solid sheets, lobules and cribriform nests, which is strikingly similar to the solid variation of adenoid cystic carcinoma, is one of the most consistent characteristics. The salivary gland type features are supported by the presence of both ductal and myoepithelial components.[4]First, it was unnamed as a tumour entity until 2013, and the WHO Head and Neck disease has only recently been classified under ICD-11 coding of malignant neoplasms of the nasal cavity & carcinoma, undifferentiated, NOS.[5]

This tumour is related to infections by specific high-risk HPV types, most commonly type 33 (~80%) and occasionally type35, 16, 52, 56, and 82. MYB rearrangements are not identified by FISH. HMSC demonstrates p40, p63, SMA and calponin (myoepithelial); KIT (CD117) (ductal); and S100 and SOX10 (both cell types). MYB IHC and MYB RNA in situ hybridisation are usually positive, despite the lack of MYB rearrangements.Diffuse p16 IHC is employed as a surrogate marker for high-risk HPV in the oropharynx.[6] Unsurprisingly, HSCs consistently exhibit robust nuclear and cytoplasmic staining in at least 70% of tumour cells. Differentials include HPV-related squamous cell carcinoma and adenoid

cystic carcinoma. The former does not harbour a salivary gland component, while the latter shows MYB or MYBL1 fusions in 60-70% of cases.[7]HMSC is restricted to the sinonasal tract in all reported cases, unlike true adenoid cystic carcinomas and harbours HPV, advocating HPV-specific testing. It has an indolent behaviour despite a typically high-grade histological appearance.[2]

Surgery still lies as the mainstay of treatment for such cases. HMSC paradoxically behaves in a relatively indolent manner with frequent local recurrences but only rare metastases and no reported tumour-related deaths, to date.[8] Therefore, it is important to diagnose this condition correctly and communicate its significance to treating clinicians.

To date, fewer than 100 well-characterised cases of HMSC have been reported in the literature (Table 1), with the majority originating from North America and Europe. Our case shares the characteristic biphasic morphology and immunophenotype described in previous series, but is noteworthy because of its presentation with unilateral epiphora and painful facial swelling associated with frontal sinus involvement and extensive ethmoidal bone destruction. These features may mimic a highly aggressive sinonasal malignancy radiologically; however, recognition of the characteristic histologic and immunohistochemical findings permits accurate classification. This case further expands the clinicopathologic spectrum of HMSC and contributes additional data from the Indian population, where reported cases remain scarce.

Table 1: Review of Literature

Year	Authors	Publication	No. of Cases	Major Contribution
2013	Justin A. Bishop et al.[10]	*Am J SurgPathol*	**8 cases**	First description of the entity as "HPV-related carcinoma with adenoid cystic carcinoma-like features"; demonstrated restriction to sinonasal tract and association with high-risk HPV.
2017	Stine Andreasen et al.[11]	*Histopathology*	**6 cases**	Expanded morphologic spectrum and clinicopathologic characterization; reinforced distinction from adenoid cystic carcinoma.
2017	Justin A. Bishop et al.[2]	*Am J SurgPathol*	**49 cases**	Largest landmark series; established the term **HMSC**. Mean age 54 years; HPV-33 in 67%; no tumor-related deaths despite high-grade morphology.
2017	Ming-Shyan Hsieh et al.[11]	*Histopathology*	**5 cases**	Expanded pathologic spectrum and confirmed HPV association.
2018	Krit Ruangritchankul et al.[12]	*Human Pathology: Case Reports*	**1 case**	First report associated with an intermediate-risk HPV genotype rather than HPV-33.
2020	Nina J. Rupp et al.[13]	*Head and Neck Pathology*	**4 cases**	Expanded morphologic and molecular spectrum; all cases

Year	Authors	Publication	No. of Cases	Major Contribution
				occurred in women.
2020	Lester D. R. Thompson[14]	*Ear Nose Throat Journal*	Review	Concise overview and recognition of HMSC as a distinct WHO entity.

CONCLUSION:MHSC is a murky tumour in a number of ways. It is made up of a bewildering variety of cellular components (hence the term multiphenotypic), which could be mistaken for squamous cell carcinoma or salivary gland carcinoma by an unsuspecting pathologist. This disengagement between phenotype and behaviour underscores the need for increasing awareness of this emerging entity, by the pathology community, so that it is not confused with its histologic mimickers and by the oncology community, so that treatment plans can be tailored appropriately.

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