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CASE STUDY

Human papillomavirus-related multiphenotypic sinonasal carcinoma – a case report

Wielofenotypowy rak zatokowo-nosowy związany z HPV – opis przypadku

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ABSTRACT:

Introduction: Human papillomavirus-related multiphenotypic sinonasal carcinoma (HMSC) is a rare cancer limited to the paranasal sinuses and nasal cavity. It is associated with HPV infection. This neoplasm is known for its relatively good prognosis compared to other histologically highly malignant sinonasal tumors.

Aim: The aim of this article is to draw attention to the HMSC as a tumor characterized by differences in the treatment as well as prognosis compared to other sinonasal cancers.

Case report: The article presents the first case of HMSC reported in the Polish literature – a 65-year-old patient with bleeding, purulent discharge, and unilateral obstruction of the nasal cavity. Differential diagnosis and the treatment pursued are discussed.

Conclusions: As a rare neoplasm, HMSC presents a challenge to both clinicians and pathologists due to its similarities to other tumors. Further studies on the expression levels of various growth factors, enzymes, and proteins within the tumor are needed for a better understanding of the biology of this cancer.

KEYWORDS: HPV virus, human papillomavirus-related multiphenotypic sinonasal carcinoma, sinonasal carcinoma

STRESZCZENIE:

Wstęp: Wielofenotypowy rak zatokowo-nosowy związany z HPV (ang. *human papillomavirus-related multiphenotypic sinonasal carcinoma*; WRZH) jest, związanym z infekcją wirusem HPV, rzadkim nowotworem, który zazwyczaj ogranicza się do zatok przynosowych i jam nosa. Odznacza się relatywnie dobrym rokowaniem w porównaniu do innych guzów zatokowo-nosowych o histologicznie wysokim stopniu złośliwości.

Cel: Zwrócenie uwagi na nowotwór, jakim jest WRZH, ze względu na różnice w leczeniu pacjentów, a także ich rokowaniu w porównaniu z innymi nowotworami.

Opis przypadku: W tym artykule zaprezentowano pierwszy opisany w polskojęzycznej literaturze medycznej przypadek WRZH – 65-letniego pacjenta z krwawieniem, ropnym wyciekiem z jam nosa oraz jego jednostronną niedrożnością. Omówiono diagnostykę różnicową oraz zastosowane leczenie.

Wnioski: WRZH jako rzadko występujący nowotwór stanowi wyzwanie zarówno dla klinicystów, jak i dla patologów ze względu na podobieństwa do innych nowotworów. Konieczne są dalsze badania poziomu ekspresji różnych czynników wzrostu, enzymów i białek w obrębie guza dla bardziej efektywnego poznania biologii tego nowotworu.

SŁOWA KLUCZOWE: rak zatokowo-nosowy, wielofenotypowy rak zatokowo-nosowy związany z HPV, wirus HPV

ABBREVIATIONS

ACC – adenoid cystic carcinoma
CT – computed tomography
HMSC – HPV-related multiphenotypic sinonasal carcinoma
HPV – high-risk human papillomaviruses
PET-CT – positron emission tomography – computed tomography
SCC – squamous cell carcinoma
WHO – World Health Organization

INTRODUCTION

High-risk human papillomaviruses (HPV) are well-known causes of head and neck cancer, responsible for the development of 20–25% of cases [1]. HPV-related multiphenotypic sinonasal carcinoma (HMSC) is a rare cancer limited to the paranasal sinuses and nasal cavities. It was first reported in the world literature in 2012 as HPV-related carcinoma with adenoid cystic carcinoma-like features [2], renamed to HMSC in 2017 [3], and subsequently listed in the 2022 WHO Classification of Head and Neck Tumours [4]. HMSC is associated with HPV infection. The HPV types isolated from the HMSC tissue material include type 16, 18, 26, 33, 35, 51, 52, 56, 68, and 82. The most common of the above, type 33, accounts for 67–84% of cases. The neoplasm presents with histological and immunophenotyping features of other cancers of the same region, including adenocarcinoma, squamous cell carcinoma, and basaloid carcinoma. Despite having the features of histological malignancy, e.g., necrosis or high mitotic index, HMSC has a favorable prognosis [3, 5–10]. It is characterized by the rate of local recurrence being higher than that of distant metastasis, which translates to a gradual clinical course and a favorable prognosis [11]. This article presents the first case of HMSC described in the Polish-language medical literature. The differential diagnosis and the patient's treatment are discussed.

CASE REPORT

A 65-year-old male patient was admitted in an emergency to the Department of Otorhinolaryngology – Head and Neck Surgery of the Medical University of Warsaw due to bleeding and purulent discharge from the nose. He had been experiencing nasal obstruction for 3 years. In addition, the patient reported experiencing a dull, splitting headache and blocked ears. Purulent discharge was found on the conjunctiva, with no associated visual disturbances. A contrast-enhanced CT scan of the nasal cavity, as acquired on the day of admission, revealed a heterogeneous mass measuring approximately 46 × 56 × 43 mm and subject to contrast enhancement. The lesion extended beyond the anterior nares, spread to the ethmoid, herniating into the frontal and maxillary sinuses, and slightly into the orbit with segmental destruction of the medial inferior wall thereof. Signs of bone destruction could be seen within the left-lateral part of the hard palate. The frontal, maxillary, and sphenoid sinuses were partially filled with mucous secretions, probably secondary to blocked outflow (Fig. 1.).

The patient had previously been diagnosed (and refused further treatment) at two other centers, where sections were collected from him for histopathological examination. The results of the examinations were discrepant. Specimens taken 8 months prior to the admission to our center showed the presence of an infiltrating low-differentiated carcinoma composed of large clusters of immature, basaloid cells, whereas a tumor infiltrate composed of small epithelioid cells was detected in specimens collected 5 months before the current admission. A large tumor filling the middle part of the nasal cavity was reported in the summary of a contrast-enhanced computed tomography (CT) scan acquired five months before the current admission. Only the patency of the upper nasal passages was preserved. Tumor infiltration did not reach the roof of the ethmoid sinus (Fig. 2.).

Ultimately, the patient agreed to the treatment due to the severity of the ailments described above. Endoscopic resection of the tumor of the nasal cavities and paranasal sinuses was performed. During the surgery, the tumor was found to have penetrated the posterior ethmoid on the right while pushing against the orbital periosteum on the left. The tumor had partially overgrown the inner wall of the lacrimal sac, which was excised. Most likely, the lesion had originated from the nasal septum. Histopathological examination of the material taken during the procedure revealed the presence of numerous, partially necrotic fragments of the nasal cavity mucosa with infiltration of pleomorphic, heterogeneous carcinoma with solid, trabecular, cribriform and papillary structures. The solid structures were made up of smaller cells formed into cribriform systems, differentiating toward myoepithelial cells. The histopathology panel was positive for CK5/6, INI-1, p40, p63, S100, SMA, calponins, p16, CK7, and Sox-10. HPV infection was diagnosed as a result of positive staining for p16 protein. Ultimately, based on the overall morphological presentation and the results of additional tests, the diagnosis of HMSC was made. A [18F] FDG PET/CT scan performed 2 weeks after the surgery showed no residual tumor in the nasal cavity and no signs of metastasis. Six months after the procedure, a CT scan revealed a radiation reaction manifested as inflammatory thickening of the mucosa (Fig. 3.).

DISCUSSION

In most cases, HMSC develops within the nasal cavity and paranasal sinuses, originating from the middle turbinate or the nasal septum [3]. To date, only three cases have been reported in other locations, including breast, vulva, and cervix [12–14].

To our knowledge, no reports on HMSC have been published in the Polish-language medical literature to date. The Polish term of *wielofenotypowy rak zatokowo nosowy związany z HPV* (abbreviation: WRZH) was proposed by the authors as a literal translation of the English name, i.e., HMSC.

According to a systematic review by Zupancic and Näsman [15], patients were diagnosed with HMSC at an average age of 53.7 years. The value was lower than that in other sinonasal cancers. The prognosis was favorable for patients who received treatment. Distant metastases were rare, and no local metastases were reported. The treatment outcomes (the patients remained under periodic follow-up) were known in 76% of cases. Out of the patients with a known treatment outcome, no recurrence occurred in 71%, with 25% of patients having experienced local recurrence, 2% died from illness, and 2% from diabetes [15].

The research data on possible gender predilection are conflicting. Some authors argue that no such predilection occurs, with both genders being equally vulnerable [7, 15, 16]. On the other hand, one study suggested that women, especially those middle-aged, have a slightly higher predisposition to develop HMSC [17].

Due to the slow progression of HMSC, patients often present for diagnosis with large tumors, more than 25% of lesions being diagnosed as stage T3 or T4 [10].

Unlike other HPV-related head and neck cancers, HMSC is not associated with smoking. On CT, HMSC is characterized by a proliferating soft tissue mass compressing the nasal structures. The lesion is well demarcated. It is subject to heterogeneous contrast enhancement, without bone infiltration. MRI presentation of HMSC usually consists of an iso- or hyperintense mass on T2-weighted scans and a heterogeneously enhanced mass on T1-weighted scans with gadolinium contrast. In contrast to adenocarcinoma (ACC), perinuclear spread is rarely observed in HMSC [10, 18].

On endoscopic examination, HMSC is visualized as well-demarcated, pedunculated or polypoid, friable masses, often originating within the posterior part of the nasal cavity [10].

Although the origin of the HMSC cells is not certain, the expression of pancytokeratin combined with biphasic staining for basaloid and myoepithelial proliferation, as well as the morphological characteristics of cells point to an origin in the salivary glands [3]. The histopathological presentation varies from case to case. Most tumors are characterized by basaloid proliferation with the presence of solid areas [15].

There is a discrepancy between the clinical nature of HMSC and its pathological features. This tumor is histologically classified as a "high malignancy" tumor despite its clinically slow growth [10]. As observed by Bishop et al. [2], the presence of highly differentiated "salivary-like" characteristic features of HMSC, which are difficult to assign to a specific category of cancer, is an important clue to the diagnosis. There are two differential diagnoses which are particularly often confused with HMSC; these include ACC and basaloid squamous cell carcinoma (SCC).

Despite the lack of a specific marker for HMSC [19], it is important that markers such as SMA, calponin, CK8, p40, p63, and c-kit be examined [8, 20]. Like basaloid squamous cell carcinoma, HMSC is often positive for SOX10 and sometimes for the S100 protein [19]. Immunohistochemical assay for p16 protein is always positive in HMSC; however, the marker is by itself not specific enough to make a diagnosis, as positivity is also observed in ACC and other tumors [2, 21]. Screening for the INI-1 marker levels verifies the presence of SMARCB1-deficient sinonasal carcinoma, whereas a negative result of the NUT assay excludes NUT carcinoma [8, 20]. In the context of the search for new and improved diagnostic markers, the results of the study by Alabiad et al. were worth mentioning [7]. The researchers demonstrated that the expression of *VEGF*, *hTERT*, and *ProExTMC* was significantly associated with age, tumor stage T3 and T4, lymph node metastasis, tumor size, recurrence, short recurrence-free survival, poor overall survival rate, and mortality. Moreover,

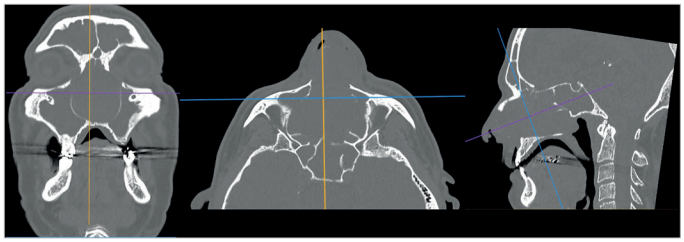


Fig. 1. CT scan without contrast enhancement. Left to right: frontal, transverse, sagittal projections.

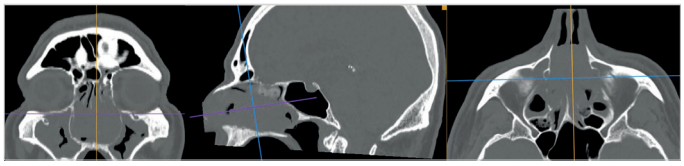


Fig. 2. CT scan without contrast enhancement. Left to right: frontal, sagittal, transverse projections.

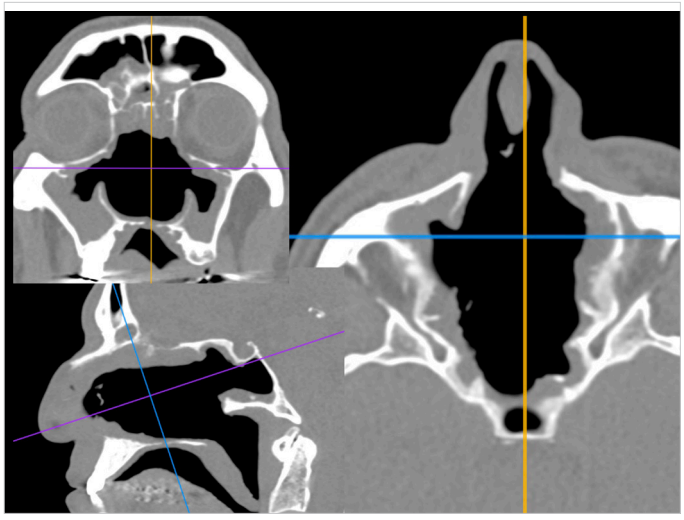


Fig. 3. CT scan acquired 6 months after the surgery: frontal, sagittal, and transverse sections.

BAX expression was significantly associated with tumor size, age, short recurrence-free survival, and recurrence. The authors suggested that these molecules could constitute novel prognostic biomarkers for targeted therapies in HMSC. On the other hand, mutations in *EP300* and *MYB* overexpression were identified in a case study by Cubides-Córdoba et al. [20]; in the opinion of the authors, both of the above could serve as molecular targets for personalized therapy.

HMSC is known for its relatively good prognosis compared to other histologically high-grade sinonasal malignancies [9]. Remodeling of sinonasal structures without aggressive invasion appears to be the hallmark of HMSC. This discovery is of great importance to surgeons as the resections may actually be easier than assumed on the basis of preoperative imaging. In most cases, endoscopic surgery with complete resection of the tumor can be pursued. Consequently, the appearance and radiological size of the HMSC tumor should not determine the choice of surgical access to the lesion. If possible, endoscopic surgery should be chosen as it improves the quality of life after surgery and reduces the risk of complications without increasing the resection margin [10].

Few cases describing HMSC treated with chemotherapy and radiotherapy are available in the literature. Rodarte et al. [22] used carboplatin and paclitaxel to treat metastatic HMSC. Subtle response to the treatment was observed, yet subsequently followed by disease progression. In another case, a combination of capecitabine, cisplatin, and docetaxel was used in palliative chemotherapy. The patient had received immunotherapy with pembrolizumab, but it was discontinued after eight cycles due to the lack of impact on disease progression on PET-CT. The patient remained on modified palliative chemotherapy with 5-fluorouracil and cetuximab [23]. In another case of an unresectable tumor, a decision was made to pursue induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil infusions, which resulted in significant tumor regression. This was followed by chemoradiotherapy with carboplatin without toxicity limits [17].

No "gold standard" or guidelines are available at present for the management of patients with HMSC. The most common procedure consists of complete surgical resection of the tumor with or without chemotherapy or radiotherapy [24]. In the case described herein, surgical resection was performed. No recurrence was observed after 8 months, and the treatment was minimally invasive for the patient.

CONCLUSIONS

- Being a rare neoplasm, HMSC poses a challenge to both clinicians and pathologists due to its similarities to other cancers. So far, no marker characteristic for this cancer has been discovered;
- Proper diagnosis of HMSC is crucial, as the malignancies that can be confused with it require much more aggressive treatment;
- More cases of HMSC should be described to gather information on the clinical features of the tumor. This should facilitate the development of an effective treatment regimen for patients;
- Further studies of the expression of various growth factors, enzymes, and proteins within the tumor are needed to better understand the biology of this cancer, develop treatment regimens, and determine prognostic factors.

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