



Case report

Human papillomavirus-related carcinoma with adenoid cystic-like features of the sinonasal tract: Case report and literature review



Zephania Saitabau Abraham^{a,*}, Caroline Philip Ngimba^b, Atuganile Edward Malango^b, Alita Mrema^c, Mwachabu Athman Saleh^d, Edda Vuhahula^e

^a Department of Surgery, School of Medicine and Dentistry, University of Dodoma, Dodoma, Tanzania

^b Department of Anatomical Pathology, Muhimbili National Hospital, Dar es Salaam, Tanzania

^c Department of Clinical Oncology, Ocean Road Cancer Institute, Dar es Salaam, Tanzania

^d Department of Radiology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

^e Department of Anatomical Pathology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

ARTICLE INFO

Keywords:

Human papillomavirus
Sinonasal tract
Adenoid cystic carcinoma
Tanzania

ABSTRACT

Introduction and importance: HPV-related carcinoma with adenoid cystic carcinoma-like features currently known as HPV-related multiphenotypic sinonasal carcinoma (HMSC) is a rare distinct head and neck high-risk HPV-related carcinoma. The high-risk HPV subtypes implicated are particularly type 33,35 and 56. So far this is the first reported rare case of a variant of sinonasal carcinoma in Tanzania.

Case presentation: We present a 59-year old female who presented with a history of right-sided nasal obstruction and intermittent epistaxis for about one year and later on had ipsilateral proptosis. A provisional diagnosis of advanced right-sided malignant sinonasal tumor was made. Trans nasal biopsy revealed HMSC.

Clinical discussion: The patient had a right sided fixed neck mass that measured about 7.5 × 8.2 cm. Magnetic resonance imaging (MRI) of the paranasal sinuses revealed a T1 weighted contrasted images that showed a huge extensive enhancing mass (estimated to measure 4.5 × 4.4) involving the nasal cavity, bilateral ethmoid sinuses, frontal and sphenoid sinuses and also the tumor exhibit intracranial extension (anterior cranial fossa) and tend to compress medial walls of both orbits though more marked on the right side. Histopathology and immunohistochemistry confirmed HPV-related multiphenotypic sinonasal carcinoma. The disease was staged to be T4bN3aM0 and the patient was referred for palliative chemoradiation.

Conclusion: Although HMSC presents at advanced stage in close to half of cases and has a high-grade histological appearance it paradoxically exhibits a relatively indolent manner with frequent local recurrences. Prompt histopathological diagnosis is important to prevent metastases and HMSC-related deaths.

1. Introduction

Human papillomavirus (HPV) is now well established as a causative agent in approximately 20–25 % of head and neck carcinomas [1,2]. HPV-related carcinomas have a strong site predilection for the oropharynx where they account for up to 80 % of squamous cell carcinomas (SCC) arising from this location [1,3]. The likelihood of detecting transcriptionally active HPV in head and neck carcinomas arising outside of the oropharynx is very low, with the notable exception of the sinonasal tract [1,4–6].

It is also estimated that 20 to 25 % of sinonasal carcinomas harbor high risk HPV including type 33,35 and 56 [4,6–8]. In the sinonasal

tract, HPV positivity is largely associated with the non-keratinizing squamous cell carcinoma phenotype [1].

HPV-related carcinomas of the head and neck tend to be predominantly squamous cell carcinomas of the non-keratinized type, but HPV positivity is not restricted to this subtype when dealing with sinonasal carcinomas. HPV analysis of a group of sinonasal carcinomas has established a distinct form of HPV-related carcinoma exhibiting features of a salivary gland carcinoma and frequently carrying the pathologic diagnosis of adenoid cystic carcinoma [5,6].

In contrast to (non-keratinizing) oropharyngeal squamous cell carcinoma or nasal vestibule squamous cell carcinoma, HMSC often shows adenoid cystic-like (biphasic) differentiation, leading to the initial

* Corresponding author.

E-mail address: zsaitabau@yahoo.com (Z.S. Abraham).

<https://doi.org/10.1016/j.ijscr.2022.107462>

Received 8 June 2022; Received in revised form 9 July 2022; Accepted 24 July 2022

Available online 28 July 2022

2210-2612/© 2022 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

description of HPV-related carcinoma with adenoid cystic-like features. A variable pattern of morphological existence of salivary-like differentiation (e.g. myoepithelial or epithelial-myoepithelial) and abrupt keratinization have been reported thus expanding the morphological spectrum of HMSCs [1,9,10].

Due to their rarity, the clinical behavior and consensus treatment guidelines pertaining HMSCs have not yet been clearly established. However, in view of the typically indolent behavior, it has been suggested that surgery with close monitoring has resulted in a good prognosis [10–12].

We are therefore reporting a rare case of an advanced variant (HMSC) of sinonasal carcinoma in an elderly patient with an indolent course. The work has been reported in line with the SCARE 2020 [13].

2. Case presentation

A 59-year old female presented to our clinic with presented with a history of right-sided nasal obstruction and intermittent epistaxis for about one year and later on reported a history of ipsilateral proptosis. Examination revealed a right-sided friable nasal mass causing deformity

of the external nose and with obvious ipsilateral proptosis. MRI of the nose and paranasal sinuses was ordered where T1 weighted contrasted images showed a huge and extensive heterogeneously enhancing mass involving the right maxillary sinus, nasal cavity, bilateral ethmoids, frontal and sphenoid sinuses with estimated size of 4.5 cm × 4.4 cm. It was seen expanding laterally to compress the medial walls of both orbits markedly on the right side where it anteriorly displaced the globe with respect to the orbit with resultant exophthalmos. Notably the intra-axial extension and invasion of the right inferior frontal pole with surrounding edema causing slight midline shift to the contralateral side was seen. Prominent and variably enlarged lymph nodes were seen on bilateral levels I and II and the largest one was seen at the right level IB estimating 1.25 cm in anterior-posterior dimensions. Constellation of findings was radiologically consistent with an extensive heterogeneously enhancing sinonasal tumor with intracranial metastasis and bilateral cervical lymphadenopathy (Fig. 1).

Trans nasal biopsy was sent for histopathology analysis. Grossly histopathologists received multiple fragments of endoscopic tissue that were whitish in colour and soft. Hematoxylin and eosin (H/E) sections showed a malignant neoplasm with areas of cribriform and tubules

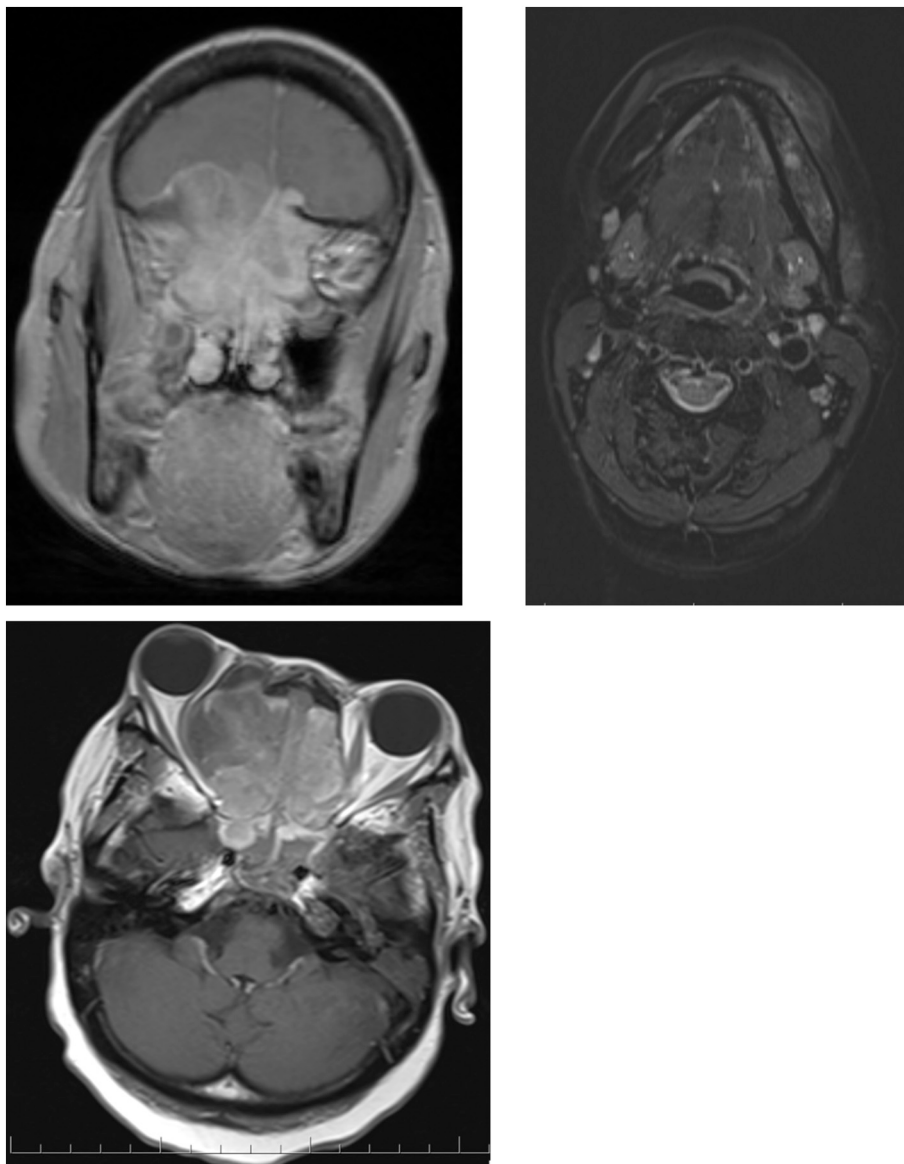


Fig. 1. T1 weighted MRI showing an extensive enhancing mass involving the nasal cavity, bilateral ethmoid sinuses, frontal and sphenoid sinuses and also the tumor exhibit intracranial extension.

formation with mucinous background. Other areas of the tumor showed solid nests comprised of polygonal cells with irregular nucleus, prominent nucleoli and eosinophilic cytoplasm. Focal areas with keratinization were noted. The differential diagnoses were adenoid cystic carcinoma, Adenosquamous carcinoma and HPV related multiphenotypic carcinoma. Immunohistochemistry done included p16 {Mouse monoclonal anti p16 (clone E6H4) Roche}, p63 {Rabbit monoclonal Anti p63 (clone EO174 Cell Marque)} and S100 {Mouse monoclonal Anti S100 (clone 4C4-9)}. The staining results from the immunohistochemistry showed diffuse and strong nuclear and cytoplasmic staining on both areas of the tumor, The p63 showed nuclear positivity on areas with squamous differentiation and was negative on areas with cribriform pattern. S100 was negative on both areas of the tumor indicating that there was no an area with myoepithelial differentiation. From the histology and immunohistochemistry results the final diagnosis of HPV-related multiphenotypic sinonasal carcinoma was established (Figs. 2–6).

Her medical history was not remarkable for cigarette smoking, alcohol consumption or orogenital sexual practices.

Results from laboratory tests revealed the following; negative HIV serology, elevated erythrocyte sedimentation rate (55/hour) and hemoglobin of 9 g/dl. Chest X-ray was found to be normal.

After thorough evaluation, she was sent to an Oncology unit at a tertiary cancer hospital for palliative chemo-radiation.

She was kept on 6 cycles of chemotherapy (intravenous cisplatin 100 mg D1 and intravenous docetaxel 120 mg D1), tablets capecitabine 1500 mg 12 hourly for 2 weeks. The cycle was repeated after every 3 weeks. She was then given a palliative radiotherapy dose at 30 Gy.

3. Discussion

Being a recently proposed disease, HPV-related carcinoma with

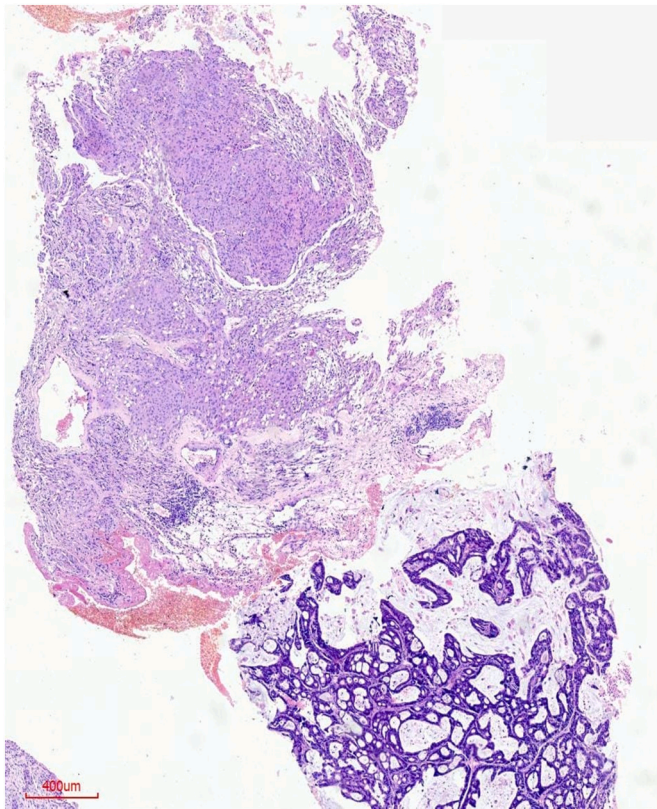


Fig. 2. Hematoxylin and Eosin (H & E) staining showing fragments of tissue with malignant neoplasm and with areas exhibiting cribriform pattern and other areas with nests of squamous cells.

adenoid cystic-like features is characterized by its resemblance with ACC in terms of certain characteristics like morphology, immunohistochemistry, its origin in the sinonasal tract and strong association with HPV type 33 [1].

The novel HPV-related carcinoma with adenoid cystic-like features was adopted in literature following description made by Bishop et al. and it was typified by solid adenoid cystic carcinoma. This new variant was later incorporated into the WHO classification of head and neck tumors [9].

The biological behavior of HMSC seems to be less aggressive than their often high-grade or highly proliferative morphology would suggest. Most of the cases present as polypoid tumors within the nasal cavity causing obstruction, facial pain and epistaxis and recurrences are frequent being encountered in up to 36 % of cases and sometimes decades (up to 30 years) after the primary diagnosis is made [14].

Differentiating HMSC from ACC or basaloid SCC may be challenging especially to junior pathologists due to presence of solid and cribriform patterns and highly cellular lesions that are composed of basaloid cells and some ductal cells. Despite HMSC resembling adenoid cystic carcinoma, it differs from ACC due to strong association with HPV [10]. Polymerase chain reaction wasn't done though in our case since the received biopsy specimen was depleted following histopathology and immunohistochemistry and thus a limitation.

Since mucosal lesions exposed to the external environment are mainly identified as HPV related carcinomas of the cervix, anus, penis, vagina and oropharynx and therefore involvement of the sinonasal tract by HPV related carcinoma seems not unusual [15].

The causative factors for the development sinonasal cancer are not well understood [1]. Wood dust and other occupational exposures are recognized risk factors, but only for a rare subtype, intestinal-type adenocarcinoma. Cigarette smoking, an important risk factor for carcinomas of most head and neck locations, has only a weak association with sinonasal carcinomas [16–19]. High-risk types of human papillomavirus (HPV) are now well established as major etiologic factors of head and neck cancer. The exact pathogenesis or entry route of these less common HPV-types to the sinonasal tract remains largely unknown [2].

Using an approach that combined HPV DNA in situ hybridization and p16 protein immunohistochemistry, high risk HPV in 21 % of sinonasal carcinomas were detected, thus establishing HPV as a significant causative factor for carcinomas arising in the nasal cavity and paranasal sinuses [5]. High risk HPV is frequently detected in the rare adenoid cystic carcinoma (ACC) arising in the cervix [20,21] and as for the head and neck high risk HPV was detected in 7 % of ACCs. Interesting, the HPV-positive cases were restricted to the sinonasal tract and exhibited a high-grade solid component [22].

Head and neck cancers including oropharyngeal SCC are examples of tumors closely associated with HPV particularly HPV type 16 and such tumors manifests clinically with extensive nodal involvement and such pattern of nodal involvement has been reported in patients with HMSC [23–25]. Despite the extensive nodal involvement in patients with HPV-related carcinoma with adenoid cystic-like features, treatment outcomes and survival scores are promising than similar HPV-negative head and neck cancer subtype [10].

Since it has been recently described, little is known about the clinical features of HPV-related carcinoma with adenoid cystic-like features in the sinonasal tract and this may have implications in delaying diagnosis of such tumors. The main strategy for treating HMSC remains to be surgery with or without chemoradiation depending on the cancer TNM (primary tumor, regional lymph nodes, distant metastasis) staging. Recurrences have been reported upon surgical excision and regional or distant metastasis is rare in patients suffering from HMSC [10]. Only two of approximately 60 reported HMSC cases (~ 3 %) presented with metastases (to the finger and lung) and no disease-specific deaths have been described from the available literature [9].

We are thus hereby reporting to the best of our knowledge the first documented rare case of HPV-related sinonasal carcinoma with adenoid

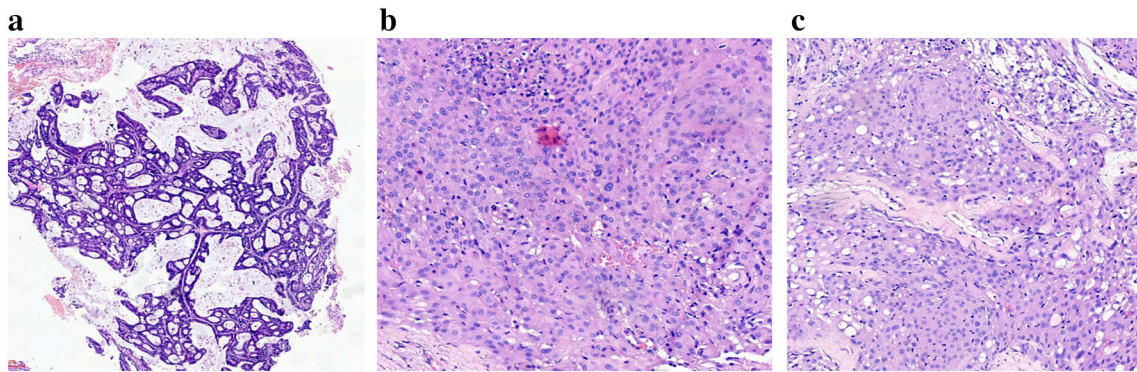


Fig. 3. a: H & E staining showing cribriform pattern and mucinous background
b: H & E staining showing large polygonal cells with eosinophilic cytoplasm, irregular nuclear membrane, coarse chromatin and prominent nucleoli.
c: H & E staining showing large polygonal cells with eosinophilic cytoplasm, irregular nuclear membrane, coarse chromatin and prominent nucleoli.

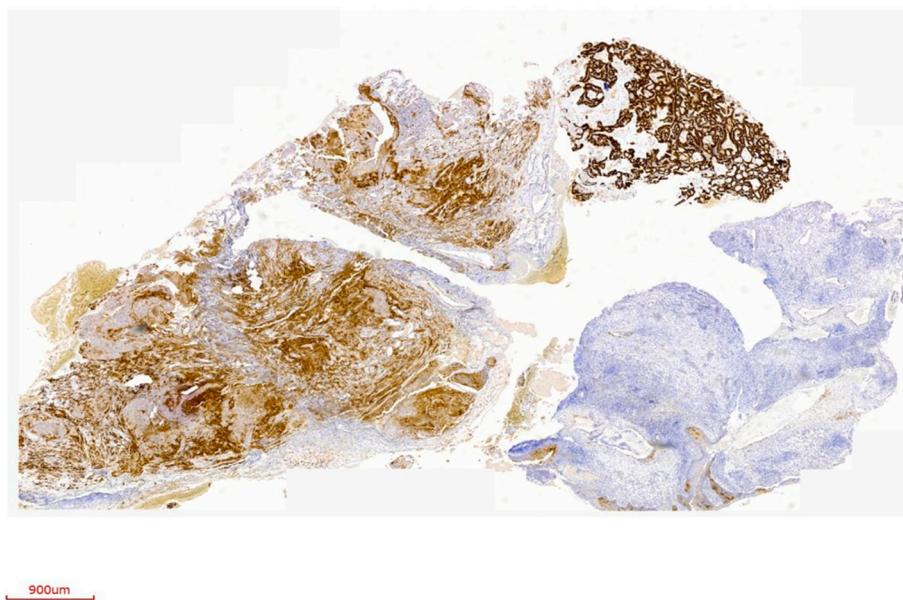


Fig. 4. p16 immunohistochemistry showing diffuse and strong nuclear and cytoplasmic staining.

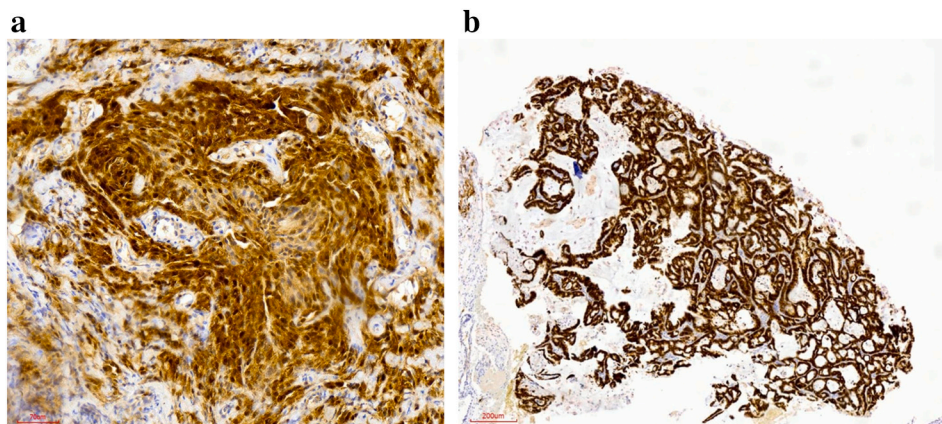


Fig. 5. (a): p16 immunohistochemistry showing diffuse and strong nuclear and cytoplasmic staining on areas with squamous differentiation.
(b): p16 immunohistochemistry showing diffuse and strong nuclear and cytoplasmic staining on areas with adenoid cystic features.

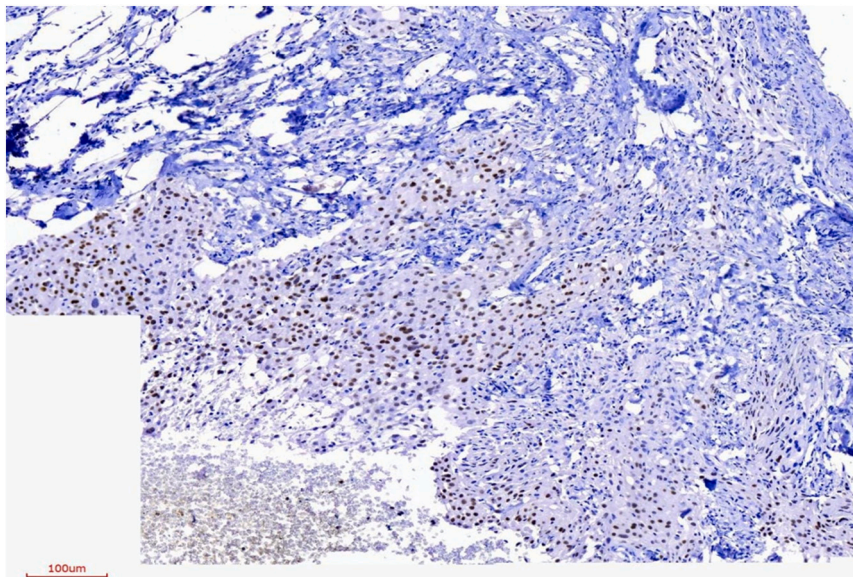


Fig. 6. p63 showing nuclear staining on areas of squamous differentiation.

cystic-like features in Tanzania that was managed by palliative chemoradiation.

4. Conclusion

HPV-related carcinoma with adenoid cystic-like features should be differentiated from sinonasal adenoid cystic carcinoma and in fact the diagnosis should be considered for any unusual-appearing carcinoma, especially if it resembles a salivary gland tumor. P16 is a useful immunohistochemical screen because all HMSCs are diffusely positive but a definitive diagnosis requires subsequent HPV-specific testing. The treatment and prognosis of HPV-related carcinoma with adenoid cystic-like features differ from those of other sinonasal carcinomas therefore an accurate diagnosis is important.

Sources of funding

None.

Ethical approval

Ethical approval was obtained from Institutional Ethics and Research Committee.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

ZSA-Conceptualization and writing original draft of the manuscript.
CPN- Conceptualization and reviewing the prepared original draft of the manuscript.

AEM- Histopathological diagnosis of the case and reviewing the prepared original draft of the manuscript.

AM- Conceptualization and reviewing the prepared original draft of the manuscript.

MAS-Conceptualization and radiological interpretation of the presented CT scan images.

EV-Histopathological diagnosis of the case and reviewing the prepared original draft of the manuscript.

Registration of research studies

N/A.

Guarantor

Dr. Zephania Saitabau Abraham takes full responsibility of the work.

Provenance and peer review

Not commissioned, externally-peer reviewed.

Declaration of competing interest

None.

Acknowledgement

Mr. Erick Philip Magorosa who is a laboratory scientist at Muhimbili National Hospital is highly acknowledged for performing immunohistochemistry.

References

- [1] J.A. Bishop, T. Ogawa, E.B. Stelow, C.A. Moskaluk, W.M. Koch, S.I. Pai, W.H. Westra, Human papillomavirus-related carcinoma with adenoid cystic-like features: a peculiar variant of head and neck cancer restricted to the sinonasal tract, *Am. J. Surg. Pathol.* 37 (6) (2013 Jun) 836.
- [2] M.L. Gillison, W.M. Koch, R.B. Capone, M. Spafford, W.H. Westra, L. Wu, M. L. Zahurak, R.W. Daniel, M. Viglione, D.E. Symer, K.V. Shah, Evidence for a causal association between human papillomavirus and a subset of head and neck cancers, *J. Natl. Cancer Inst.* 92 (9) (2000 May 3) 709–720.
- [3] A.D. Singhi, W.H. Westra, Comparison of human papillomavirus in situ hybridization and p16 immunohistochemistry in the detection of human papillomavirus-associated head and neck cancer based on a prospective clinical experience, *Cancer* 116 (9) (2010 May 1) 2166–2173.
- [4] L. Alos, S. Moyano, A. Nadal, I. Alobid, J.L. Blanch, E. Ayala, B. Lloveras, W. Quint, A. Cardesa, J. Ordi, Human papillomaviruses are identified in a subgroup of sinonasal squamous cell carcinomas with favorable outcome, *Cancer* 115 (12) (2009 Jun 15) 2701–2709.
- [5] J.A. Bishop, T.W. Guo, D.F. Smith, H. Wang, T. Ogawa, S.I. Pai, W.H. Westra, Human papillomavirus-related carcinomas of the sinonasal tract, *Am. J. Surg. Pathol.* 37 (2) (2013 Feb) 185.

- [6] S.K. El-Mofty, D.W. Lu, Prevalence of high-risk human papillomavirus DNA in nonkeratinizing (cylindrical cell) carcinoma of the sinonasal tract: a distinct clinicopathologic and molecular disease entity, *Am. J. Surg. Pathol.* 29 (10) (2005 Oct 1) 1367–1372.
- [7] J. Laco, K. Siegllová, H. Vošmiková, P. Dundr, K. Němejcová, J. Michálek, P. Čelakovský, V. Chrobok, R. Mottl, A. Mottlová, L. Tuček, The presence of high-risk human papillomavirus (HPV) E6/E7 mRNA transcripts in a subset of sinonasal carcinomas is evidence of involvement of HPV in its etiopathogenesis, *Virchows Arch.* 467 (4) (2015 Oct) 405–415.
- [8] A.B. Larque, S. Hakim, J. Ordi, A. Nadal, A. Diaz, M.D. Pino, L. Marimon, I. Alobid, A. Cardesa, L. Alos, High-risk human papillomavirus is transcriptionally active in a subset of sinonasal squamous cell carcinomas, *Mod. Pathol.* 27 (3) (2014 Mar) 343–351.
- [9] J.A. Bishop, S. Andreasen, J.F. Hang, M.J. Bullock, T.Y. Chen, A. Franchi, J. Garcia, D.R. Gnepp, C.R. Gomez-Fernandez, S. Ihrler, Y.J. Kuo, HPV-related multiphenotypic sinonasal carcinoma: an expanded series of 49 cases of the tumor formerly known as HPV-related carcinoma with adenoid cystic carcinoma-like features, *Am. J. Surg. Pathol.* 41 (12) (2017 Dec) 1690.
- [10] S.J.i. Hwang, S. Ok, H.M. Lee, E. Lee, I.H. Park, Human papillomavirus-related carcinoma with adenoid cystic-like features of the inferior turbinate: a case report, *Auris Nasus Larynx.* 42 (1) (2015 Feb) 53–55.
- [11] A.I. Rodarte, A.S. Parikh, S.K. Gadkaree, A.E. Lehmann, W.C. Faquin, E. H. Holbrook, D.T. Lin, Human papillomavirus related multiphenotypic sinonasal carcinoma: report of a case with early and progressive metastatic disease, *J. Neurol. Surg. Rep.* 80 (04) (2019 Oct) e41–e43.
- [12] R.J. Chouake, M. Cohen, A.M. Illoreta, Case report: HPV-related carcinoma with adenoid cystic-like features of the sinonasal tract, *Laryngoscope* 128 (7) (2018 Jul) 1515–1517.
- [13] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, A. Kerwan, A. Thoma, A.J. Beamish, A. Noureldin, A. Rao, B. Vasudevan, B. Challacombe, The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines, *Int. J. Surg.* 1 (84) (2020 Dec) 226–230.
- [14] N.J. Rupp, U. Camenisch, K. Seidl, E.J. Rushing, N. Anderegg, M.A. Broglie, D. Holzmann, G.B. Morand, HPV-related multiphenotypic sinonasal carcinoma: four cases that expand the morpho-molecular spectrum and include occupational data, *HeadNeck Pathol.* 14 (3) (2020 Sep) 623–629.
- [15] J.T. Lewis, A.M. Oliveira, A.G. Nascimento, D. Schembri-Wismayer, E.A. Moore, K. D. Olsen, J.G. Garcia, M.L. Lonzo, J.E. Lewis, Low-grade sinonasal sarcoma with neural and myogenic features: a clinicopathologic analysis of 28 cases, *Am. J. Surg. Pathol.* 36 (4) (2012 Apr 1) 517–525.
- [16] D. Luce, A. Leclerc, D. Bégin, P.A. Demers, M. Gérin, E. Orlowski, M. Kogevinas, S. Belli, I. Bugel, U. Bolm-Audorff, L.A. Brinton, Sinonasal cancer and occupational exposures: a pooled analysis of 12 case-control studies, *Cancer Causes Control* 13 (2) (2002 Mar) 147–157.
- [17] A. d'Errico, S. Pasian, A. Baratti, R. Zanelli, S. Alfonzo, L. Gilardi, F. Beatrice, A. Bena, G. Costa, A case-control study on occupational risk factors for sino-nasal cancer, *Occup. Environ. Med.* 66 (7) (2009 Jul 1) 448–455.
- [18] P.A. Demers, M. Kogevinas, P. Boffetta, A. Leclerc, D. Luce, M. Gérin, G. Battista, S. Belli, U. Bolm-Audorf, L.A. Brinton, D. Colin, Wood dust and sino-nasal cancer: pooled reanalysis of twelve case-control studies, *Am. J. Ind. Med.* 28 (2) (1995 Aug) 151–166.
- [19] D. Luce, M. Gérin, A. Leclerc, J.F. Morcet, J. Brugère, M. Goldberg, Sinonasal cancer and occupational exposure to formaldehyde and other substances, *Int. J. Cancer* 53 (2) (1993 Jan 21) 224–231.
- [20] A.V. Parwani, A.E. Sehdev, R.J. Kurman, B.M. Ronnett, Cervical adenoid basal tumors comprised of adenoid basal epithelioma associated with various types of invasive carcinoma: clinicopathologic features, human papillomavirus DNA detection, and P16 expression, *Hum. Pathol.* 36 (1) (2005 Jan 1) 82–90.
- [21] Y.J. Yang, G.B. Gordon, Cervical adenoid cystic carcinoma coexisting with multiple human papillomavirus-associated genital lesions, *Gynecol. Obstet. Investig.* 47 (4) (1999) 272–277.
- [22] J.M. Boland, E.D. McPhail, J.J. Garcia, J.E. Lewis, D.J. Schembri-Wismayer, Detection of human papilloma virus and p16 expression in high-grade adenoid cystic carcinoma of the head and neck, *Mod. Pathol.* 25 (4) (2012 Apr) 529–536.
- [23] A.K. Chaturvedi, Epidemiology and clinical aspects of HPV in head and neck cancers, *HeadNeck Pathol.* 6 (1) (2012 Jul) 16–24.
- [24] M.E. Sabatini, S. Chiocca, Human papillomavirus as a driver of head and neck cancers, *Br. J. Cancer* 122 (3) (2020 Feb) 306–314.
- [25] P.T. Hennessey, W.H. Westra, J.A. Califano, Human papillomavirus and head and neck squamous cell carcinoma: recent evidence and clinical implications, *J. Dent. Res.* 88 (4) (2009 Apr) 300–306.