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Case Report

Poorly differentiated sinonasal neuroendocrine carcinoma with skull base invasion: A case report

Jonathan Ramos-Escalante[1], José Alfonso Alvarez-Castro[1], Marcos V. Sangrador-Deitos[1], Gerardo Yoshiaki Guinto-Nishimura[2], Ricardo Marian-Magaña[1], Jorge A. Lara-Olivas[1], Jesús Daniel Rembao-Bojórquez[3], Juan Luis Gomez-Amador[1]

[1]Department of Neurosurgery, National Institute of Neurology and Neurosurgery, [2]Department of Neurosurgery, Hospital de Especialidades Centro Médico Nacional Siglo XXI, [3]Department of Pathology, National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez", Mexico City, Mexico.

E-mail: Jonathan Ramos-Escalante - jonathanramos.10@hotmail.com; José Alfonso Alvarez-Castro - alfonso.alvarez@innn.edu.mx; *Marcos V. Sangrador-Deitos - marcos_5949@hotmail.com; Gerardo Yoshiaki Guinto-Nishimura - guintongy@gmail.com; Ricardo Marian-Magaña - ricardomarian@neurocirugia-innn.com; Jorge A. Lara-Olivas - larajorge96@hotmail.com; Jesús Daniel Rembao-Bojórquez - drembao@innn.edu.mx; Juan Luis Gomez-Amador - jlga@neurocirugia-innn.com

***Corresponding author:**
Marcos V. Sangrador-Deitos, Department of Neurosurgery, National Institute of Neurology and Neurosurgery, Mexico City, Mexico.

marcos_5949@hotmail.com

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ABSTRACT

Background: Sinonasal neuroendocrine carcinoma is a rare head and neck tumor that represents only 5% of sinonasal neoplasms. This lesion has a high risk of invasion to adjacent structures such as the orbit, skull base, and soft tissues, with symptoms usually being nonspecific. Most cases are diagnosed in late stages, decreasing overall survival without treatment. To date, there is no consensus on management given its low prevalence; however, it has been shown that multimodal therapy, with the correct surgical approach as the mainstay, offers a better disease-free prognosis.

Case Description: A 46-year-old woman presented with a 1 year history of nasal symptoms, characterized by obstruction and epistaxis. Imaging studies showed an extra-axial mass causing skull base erosion and displacement of the right fronto-orbital region, without invasion of brain parenchyma or meninges. A biopsy was performed and an unresectable poorly differentiated sinonasal neuroendocrine carcinoma was diagnosed. Treatment with radio and chemotherapy was initiated and, as the tumoral volume decreased, she was referred for neurosurgical intervention; an endonasal endoscopic approach was performed. Gross total resection was achieved and the patient was discharged without postoperative complications and no residual lesion on imaging.

Conclusion: We describe the evolution of a rare advanced-stage neoplasm. It highlights that despite receiving an initial diagnosis of an unresectable mass, multimodal therapy, and an adequate surgical approach deemed the entire lesion to be resected. Despite the favorable clinical evolution, the follow-up of neuroendocrine carcinoma is prioritized as a neoplasm with a high rate of recurrence and metastasis.

Keywords: Carcinoma, Neuroendocrine, Neurosurgery, Sinonasal, Skull base neoplasms

INTRODUCTION

Neuroendocrine tumors (NET) are a rare type of cancer that develops in cells of the neuroendocrine system. It is estimated that more than 12,000 people in the United States are diagnosed with a NET yearly, and approximately 175,000 live with this diagnosis.[6] The particular

characteristic of NET is that their cells release hormones into the bloodstream in response to signals from the nervous system.[15] Besides, the etiology of NET is largely unknown, except in certain hereditary genetic syndromes, such as multiple endocrine neoplasia types 1 and 2, Von Hippel-Lindau syndrome, and tuberous sclerosis (TSC1 and TSC2).[19] NET can develop in various parts of the body, including the head and neck.

Neuroendocrine carcinomas (NECs) are a rare and aggressive type of NET that overgrows and spreads systemically.[4] NEC in the head and neck is particularly rare and often has a poor prognosis. Sinonasal neuroendocrine differentiation accounts for only 5% of all neoplasms in this region; it was first described 30 years ago, and by 2016, only 242 published cases were found.[11]

The symptoms of NEC in the head and neck can vary depending on the location of the tumor. Some common symptoms include pain, swelling, and difficulty swallowing or speaking.[9,17] The diagnosis of NEC typically involves a combination of imaging tests, laboratory tests, and biopsies that help classify NEC into subtypes based on cytomorphological characteristics, such as small cells and large cells. Head and neck NEC usually do not have abnormal p53 expression or a lack of retinoblastoma (RB) reactivity.[16]

According to the new 2022 5th Ed. World Health Organization Classification of Tumors of the Head and Neck, sinonasal NEC is negative for squamous markers such as p40 and cytokeratin (CK)5/6, with low expression of SMARCA4 but preserved expression of SMARCB1. These tumors continue to be characterized by patterns comprising nests, ribbons, and rosettes; they are also positive for neuroendocrine markers like CD56, synaptophysin, chromogranin, neuron-specific enolase, and CK AE1/AE3. Poorly differentiated NECs are still divided into small-cell type and large-cell type; both are aggressive with a 5-year survival rate of 20.8–21.7% and unknown ideal treatment.[20,21]

Treatment options for NEC may include surgery, radiotherapy (RT), chemotherapy (QT), or a combination of these approaches.[3] The choice of treatment will depend on the location and size of the tumor, as well as the stage of the disease and the patient's overall status.

This report presents a rare case of primary poorly differentiated sinonasal NEC with invasion of the neurocranium. It was treated multimodally with chemo (QT)/RT and surgery, with successful gross total resection.

CASE PRESENTATION

We present the case of a 46-year-old female with a history of hysterectomy for a high-grade squamous intraepithelial lesion in the cervix, several allergies, and seasonal rhinitis treated with montelukast. She presented with sudden posterior epistaxis that was partially treated with nasal packing. She underwent a first endonasal biopsy that reported an unresectable tumor in the right nasal cavity, with negative markers for esthesioneuroblastoma; a microscopic focus of poorly differentiated carcinoma with positive CKAE1/AE3 and negative CD56 and PS100 was reported [Figure 1].

Treatment was started with three cycles of cisplatin-based chemotherapy and radical RT in two phases. The first RT phase consisted of 45 Gy in 25 fractions to the neck and primary lesions. Subsequently, a second biopsy was obtained, which contained residual microscopic foci of poorly differentiated carcinoma, with lymphatic and vascular permeation associated with extensive necrosis and fibrosis due to RT. The second phase of RT consisted of 23 Gy in 12 fractions, resulting in tumor shrinkage. Finally, maintenance therapy with biweekly cetuximab was started.

Afterward, magnetic resonance imaging (MRI) was performed [Figure 2], revealing an extra-axial mass that caused skull base erosion, and displacement of the right frontal orbital region, without invasion of brain parenchyma or meninges. The lesion occupied the right nostril, invading the right maxillary, ethmoidal, sphenoidal, and frontal sinuses and extending into the ipsilateral orbital cone. A subsequent positron emission tomography (PET)/computed tomography CT scan reported hypermetabolism in the right nasal structures without systemic dissemination or cervical lymph node metastasis.

Clinically, she reported a right hemicranial headache with a visual analog scale of 8/10, paresthesias in the ipsilateral hemiface, weight loss, vertigo, persistent nasal congestion, anosmia, and neuropathic pain in the extremities. At anterior rhinoscopy, a grayish polypoid mass was found in Cottle Zone III, occupying the entire right nostril. The neurological evaluation showed mild dysarthria, impaired judgment, no abstraction capacity, anosmia, an afferent pupillary defect in the right eye, and hypomimia.

She was transferred to the operating room and placed in a supine position. The head was fixed on a Mayfield headset and rotated 15° to the left; a bicoronal Soutar incision was performed. The surgical strategy was an endoscopic-transcribiform resection with pericranial plasty in two surgical stages. At first, the neuro-otology team performed an endoscopic examination with a 0° rigid lens to resect the calcified portion of the tumor with a chisel and continue with its demassification. In the second stage, the neurosurgical team continued with resection from the lateral wall and floor of the nasal cavity. A Draff III procedure was performed for anterior skull base dissection, communicating the frontal sinuses with the nasal cavity [Figure 3]. A soft intracranial lesion was completely resected, which presented mild infiltration of the right rectus gyrus. To repair the defect,

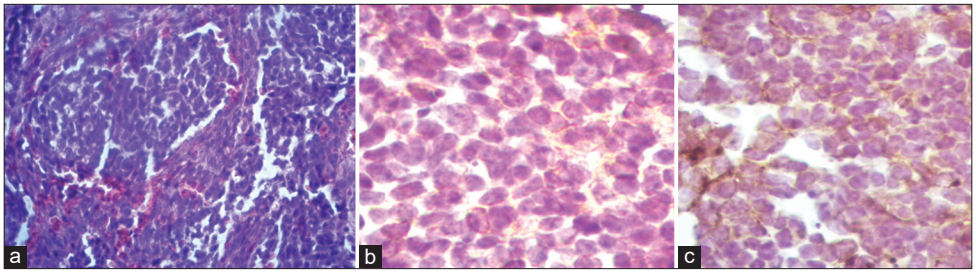

Figure 1: Histopathology. Poorly differentiated sinonasal neuroendocrine carcinoma. (a) This poorly differentiated tumor grows in nests and trabeculae of cells; the tumor is composed of small to medium sized cells with hyperchromatic nuclei and numerous mitoses. (b and c) Immunohistochemistry: Expression of low molecular weight cytokeratin and chromogranin, respectively.

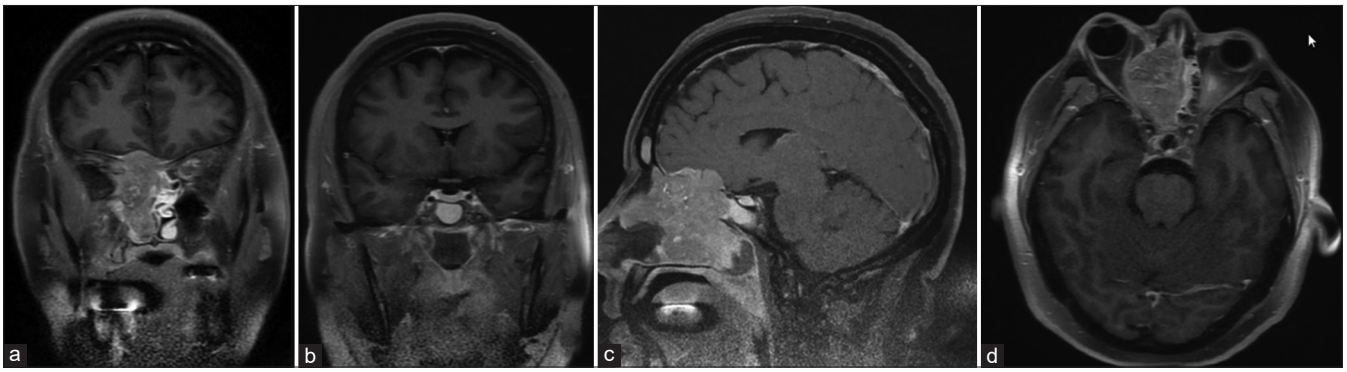

Figure 2: Preoperative magnetic resonance imaging. Coronal T1WI (a and b), sagittal T1WI (c), and axial T1WI. A noncalcified heterogeneous mass with origin in the right nasal cavity with irregular infiltration to ipsilateral ethmoid cells and orbit, causing nasal septum displacement and skull base erosion, with slight frontal lobe displacement can be observed. Uninvolved pituitary gland and sellar region are shown in Figure 1b.

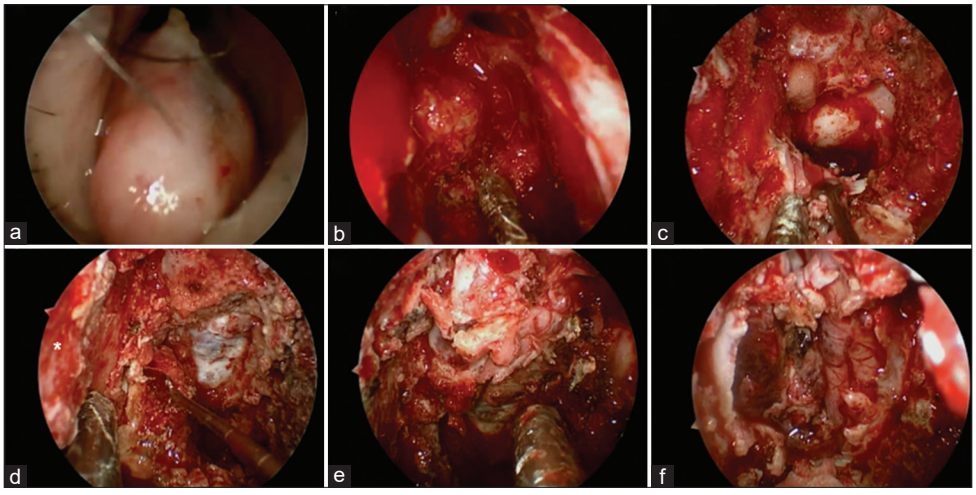

Figure 3: Intraoperative images. The tumor was bulging through the right nare (a) and was largely calcified, occupying the entire nasal cavity (b). After drilling the osseous portion of the tumor, the sella and anterior fossa were exposed (c). Further, drilling was carried out until exposure of the anterior fossa and orbit (asterisk) was achieved (d). The tumor invading the anterior fossa was dissected up to the normal dural margins (e). Complete removal of the intradural portion of the tumor was achieved (f).

the dural substitute was placed in an inlay fashion followed by autologous fascia lata; pericranium was extracted from a previous bicoronal incision, and it was used to finally cover the defect [Figure 4].

The patient presented an uneventful postoperative course with symptomatic improvement; an MRI was conducted [Figure 5], finding no residual lesion or compromise of adjacent structures. Given the extension of the tumor, she was evaluated by the neuroendocrinology staff, which found no evidence of biochemical alteration of pituitary hormones. One week later, she presented a transnasal cerebrospinal fluid fistula, which was successfully treated with antibiotics, lumbar drainage, and acetazolamide, with no clinical evidence of infection, after which, she was discharged. To date, the patient maintains an adequate quality of life 1 year after the onset of symptoms.

DISCUSSION

Sinonasal undifferentiated NEC is relevant because the only current factor in response to treatment and survival is histological grade; suspicion is limited to nonspecific symptoms even in advanced stages, and the majority of cases (75.0–84.6%) are diagnosed at stage IV,[11,17,23] when there is already invasion to the skull base, orbit, or brain. Its prevalence peaks between the 5th and 6th decades of life, with a slight male predisposition;[11] however, there are no identified risk factors.

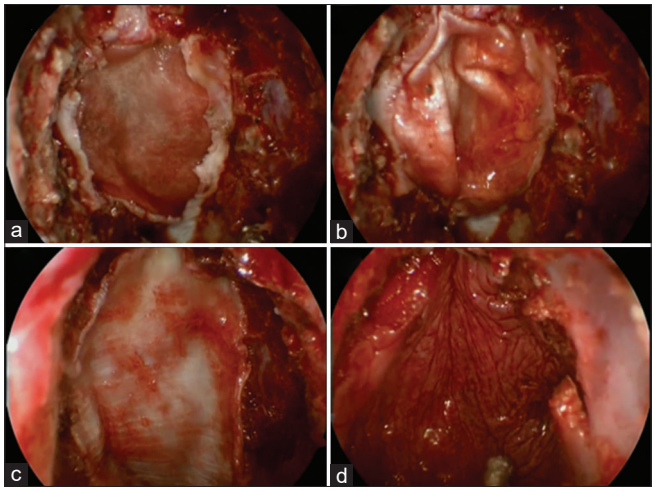

Figure 4: Reconstruction. After tumor removal, multilayered reconstruction was performed using an inlay dural substitute (a) and fascia lata graft (b) followed by an onlay fascia lata graft (c). An anteriorly based pedicled pericranial flap was harvested from a bicoronal incision and advanced through the nasion to cover the defect (d).

Regarding diagnosis, CT or MRI imaging is imperative for evaluating the extent of local invasion and metastasis. Spread to lymph nodes is particularly rare and only occurs in 10–20% of sinonasal tumors;[13] in this patient, no clinically suspicious cervical adenopathies were found, and pre-surgical PET/CT did not demonstrate active lymphatic metastases. Calcification and hemorrhage are rare features in these lesions, although bone destruction has been a common finding.[23] The incidence of ectopic hormone secretion of adrenocorticotropic hormone (ACTH), calcitonin, serotonin, vasopressin, and β-melanocyte-stimulating hormone (MSH) is as low as 1.4%;[17] however, there is still no consensus to incorporate these biomarkers as routine studies to rule out an initial paraneoplastic syndrome.

Due to its low incidence and few comparative studies, there is no available standardized therapeutic algorithm. Lesions confined to the nasal cavity are essentially surgical, leaving QT and RT for unresectable tumors, noncandidates for surgery, and metastatic or residual disease.[4] Regarding poorly differentiated carcinomas, there is a clear benefit of surgery plus RT, with or without QT, referring to a trimodal therapy with good outcomes. In a meta-analysis, the combination of surgery, RT, and QT for this histologic subtype resulted in statistically significant longer survival (OR 0.368; 95% CI 0.147–0.921).[22] Other analyses have demonstrated a complete response derived from induction QT for chemosensitization of neoplastic cells before RT or surgery, preserving more healthy tissue and achieving better overall survival.[8] Recent local literature has reported the treatment of moderately differentiated noninvasive

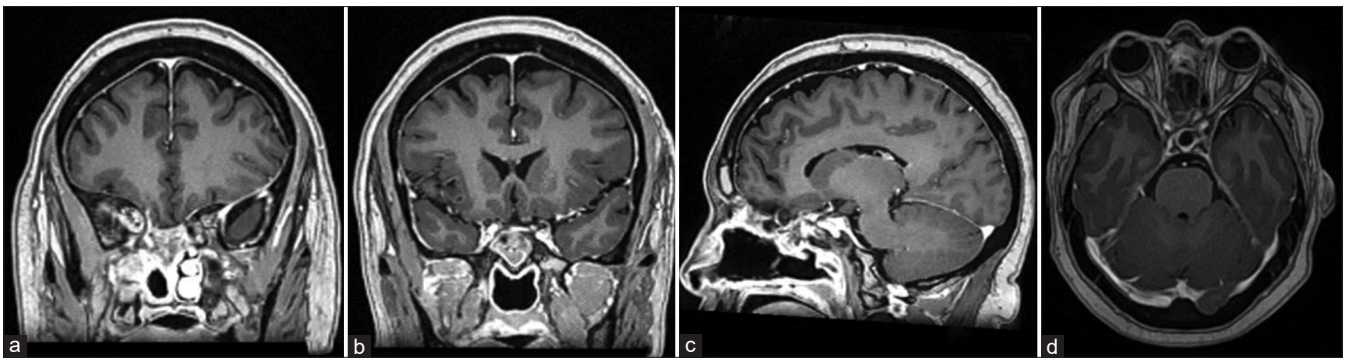

Figure 5: Postoperative magnetic resonance imaging. Coronal T1WI C+ (a and b), sagittal T1WI C+ (c), and axial (d), T1WI C+. No residual lesion or evidence of skull base involvement is observed. The straight gyri of both frontal lobes present areas of encephalomalacia, without evidence of abnormal enhancements.

sinonasal NEC, based on surgery and QT with etoposide and cisplatin, with no evidence of recurrence and good quality of life (Karnofsky 90% and eastern cooperative oncology group (ECOG) 0).[4] In agreement with the aforementioned studies, this patient had a satisfactory initial response to RT for a poorly differentiated tumor initially considered unresectable; moreover, the surgical approach succeeded in resecting the entire lesion, including its extension to the brain.

Neurosurgery remains the mainstay of treatment; however, the decision of whether to use a transcranial, endoscopic, or combined approach is related to both oncological and individualized criteria. In the case of intracranial extension of potentially aggressive tumors, like in this case, the exclusive endoscopic approach is associated with limited morbidity, but a frontal craniotomy provides better control of surgical margins in locally advanced neoplasms and recurrence.[5,12] It has been proposed that for lesions that invade the rectus gyrus and medial orbital gyrus, the open approach should be chosen; however, the adequate postoperative outcome of our patient was completely matched by a pure endoscopic approach, reducing hemorrhagic, ophthalmologic, and infectious complications found in the open surgery. Regarding the treatment of persistent high-grade lesions, salvage resection has been shown to be a potentially curative option; one cohort demonstrated a disease-free survival of 60% following salvage surgery.[11]

Orbital invasion and intracranial extension of the sinonasal tumor are recognized as the worst prognostic factors due to the difficulty in obtaining negative surgical margins, and the high risk of systemic dissemination through dural infiltration.[1,12] Accordingly, achieving free margins is the primary objective, regardless of the technique used to reach it. Novel endonasal techniques focus on creating an optimal surgical corridor for a wider scope of visualization through lamina papyracea removal, and drilling crista galli, among other techniques that allow a better inspection of the sinus and improve surgical margins.[10,14] In our patient, even when the lesion extended to the orbit and neurocranium, removal of bony structures through the Draf III procedure helped to establish adequate resection margins with a successful endoscopic tumor removal, and including an appropriate multi-layered watertight closure for skull base reconstruction led to a reduction of the sequelae.

Among the new molecular therapies, isocitrate dehydrogenase (IDH)2 mutations have been found as a potential therapeutic target for sinonasal NEC, reporting a prevalence ranging from 11% to 83% in different case series. Enasidenib is an anti-IDH2 agent that could be incorporated into the therapeutic regimen for recurrent lesions.[7] In addition, a recent cohort analysis found the use of octreotide, a somatostatin analog, as an effective antiproliferative treatment in residual low-grade lesions after surgery;[11] however, it has not yet been fully studied.

Surveillance is essential given the high recurrence and metastasis rates of up to 70–80%, and the average survival of 2–3 years. Endocrine syndrome with elevated serum antidiuretic hormone (ADH) and ACTH levels is a failure predictor of local control and poor prognosis,[2] which was not seen in the postoperative biochemical evaluation of this patient. However, the low degree of histologic differentiation found has been associated with overall survival as low as 30.8–40.0% at 5 years in representative studies.[11,22] Some other negative prognostic factors reported are high TNM stage, lymph node metastasis, Ki-67> 55%, and skull base infiltration[18] which give greater relevance to the follow-up of this patient.

CONCLUSION

Poorly differentiated sinonasal NEC with skull base invasion is a rare and aggressive type of cancer that can cause a wide range of symptoms and complications. In this case, the diagnosis was made incidentally after finding recurrent epistaxis; further, examination revealed a tumor in the nasal cavity that invaded the skull base. Usually, the approach for this type of cancer involves RT and QT; finally, if the tumor does not respond to this treatment and invades other areas, resection is necessary. Despite the aggressive nature of this cancer, the patient responded well to treatment and experienced a significant improvement in symptoms.

Overall, this case report highlights the importance of early detection and prompt treatment in improving the outcomes for patients with this specific pathology. It also underscores the need for further research to better understand this rare and complex disease and to develop more effective treatment strategies.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Albonette-Felicio T, Rangel GG, Martinéz-Pérez R, Hardesty DA, Carrau RL, Prevedello DM. Surgical management of anterior skull-base malignancies (endoscopic vs. Craniofacial resection). J Neurooncol 2020;150:429-36.
2. Babin E, Rouleau V, Vedrine PO, Toussaint B, de Raucourt D, Malard O, *et al.* Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. J Laryngol Otol 2006;120:289-97.
3. Bouzbouz A, Abdulhakeem B, Laababsi R, Rouadi S, Abada R, Roubal M, *et al.* Rare cases of head and neck's neuroendocrine carcinomas disease: Case series of 4 patients and review of the literature. Int J Surg Case Rep 2020;66:270-6.
4. Busto-Ruano JP, Romo-Magdaleno JA, Mora-Mendoza I, Alanis-Nuñez AJ, de Luna-Sánchez MP, Sánchez-Santa Ana JR. Nasal cavity moderetely differentiated neuroendocrine carcinoma (atypical carcinoid): Case report and literature review. Rev Sanid Milit 2021;75:1-8.
5. Chatelet F, Simon F, Bedarida V, Le Clerc N, Adle-Biassette H, Manivet P, *et al.* Surgical management of sinonasal cancers: A comprehensive review. Cancers (Basel) 2021;13:3995.
6. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, *et al.* Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017;3:1335-42.
7. Esposito A, Stucchi E, Baronchelli M, Di Mauro P, Ferrari M, Lorini L, *et al.* Molecular basis and rationale for the use of targeted agents and immunotherapy in sinonasal cancers. J Clin Med 2022;11:6787.
8. Issa K, Ackall F, Jung SH, Li J, Jang DW, Rangarajan SV, *et al.* Survival outcomes in sinonasal carcinoma with neuroendocrine differentiation: A NCDB analysis. Am J Otolaryngol 2021;42:102851.
9. Kao HL, Chang WC, Li WY, Chia-Heng Li A, Fen-Yau Li A. Head and neck large cell neuroendocrine carcinoma should be separated from atypical carcinoid on the basis of different clinical features, overall survival, and pathogenesis. Am J Surg Pathol 2012;36:185-92.
10. Kasemsiri P, Prevedello DM, Otto BA, Old M, Filho LD, Kassam AB, *et al.* Endoscopic endonasal technique: Treatment of paranasal and anterior skull base malignancies. Braz J Otorhinolaryngol 2013;79:760-79.
11. Keilin CA, VanKoevering KK, McHugh JB, McKean EL. Sinonasal neuroendocrine carcinoma: 15 years of experience at a single institution. J Neurol Surg B Skull Base 2023;84:51-9.
12. López F, Shah JP, Beitler JJ, Snyderman CH, Lund V, Piazza C, *et al.* The selective role of open and endoscopic approaches for sinonasal malignant tumours. Adv Ther 2022;39:2379-97.
13. López-Hernández A, Vivanco B, Franchi A, Bloemena E, Cabal VN, Potes S, *et al.* Genetic profiling of poorly differentiated sinonasal tumours. Sci Rep 2018;8:3998.
14. Lund VJ, Wei WI. Endoscopic surgery for malignant sinonasal tumours: An eighteen year experience. Rhinology 2015;53:204-11.
15. Meacham R, Matrka L, Ozer E, Ozer HG, Wakely P, Shah M. Neuroendocrine carcinoma of the head and neck: A 20-year case series. Ear Nose Throat J 2012;91:E20-4.
16. Mete O, Wenig BM. Update from the 5th edition of the World Health Organization classification of head and neck tumors: Overview of the 2022 WHO classification of head and neck neuroendocrine neoplasms. Head Neck Pathol 2022;16:123-42.
17. Mitchell EH, Diaz A, Yilmaz T, Roberts D, Levine N, DeMonte F, *et al.* Multimodality treatment for sinonasal neuroendocrine carcinoma. Head Neck 2012;34:1372-6.
18. Peng J, Li X, Liu Z, Cui Z, Jin H. Clinical analysis of 31 patients with sinonasal neuroendocrine carcinoma. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2022;36:32-5.
19. Shah MH, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P, *et al.* Neuroendocrine and adrenal tumors, Version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2021;19:839-68.
20. Thawani R, Kim MS, Arastu A, Feng Z, West MT, Taflin NF, *et al.* The contemporary management of cancers of the sinonasal tract in adults. CA Cancer J Clin 2023;73:72-112.
21. Thompson LD, Bishop JA. Update from the 5th edition of the World Health Organization classification of head and neck tumors: Nasal cavity, paranasal sinuses and skull base. Head Neck Pathol 2022;16:1-18.
22. Van der Laan TP, Iepsma R, Witjes MJ, van der Laan BF, Plaat BE, Halmos GB. Meta-analysis of 701 published cases of sinonasal neuroendocrine carcinoma: The importance of differentiation grade in determining treatment strategy. Oral Oncol 2016;63:1-9.
23. Zhu Q, Zhu W, Wu J, Zhang H. The CT and MRI observations of small cell neuroendocrine carcinoma in paranasal sinuses. World J Surg Oncol 2015;13:54.

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