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Sinonasal undifferentiated carcinoma arising coexistently with inverted papilloma

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A case of sinonasal undifferentiated carcinoma (SNUC) arising concomitantly with inverted papilloma is presented. The patient is a 50-year-old Thai male. Histomorphological features of the tumor include medium-sized neoplastic cells arranged in cords, nests and sheets with numerous mitosis and massive necrosis. Areas of inverted papilloma with dysplastic changes were observed. The patient underwent radiotherapy and chemotherapy, and no evidence of disease was detected at the last follow-up, 5 months after the initial management. Sinonasal undifferentiated carcinoma has been recognized as a distinctive entity since 1986. It is an aggressive disease which results in death of most patients within 1 year after the diagnosis. Morphologically, SNUC exhibits two main histological variants, western type and nasopharyngeal cell type. The latter is exclusively encountered among Asian populations and has stronger association with Ebstein-Barr Virus. The tumor should be treated aggressively with combined multimodal methods. To the best of our knowledge, this is the first case of sinonasal undifferentiated carcinoma arising coexistently with inverted papilloma.

Keywords: *Sinonasal Undifferentiated carcinoma, Sinonasal tract carcinoma, Inverted papilloma.*

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บทความนี้เป็นการนำเสนอผู้ป่วยชายหนึ่งรายอายุ 50 ปี ซึ่งป่วยเป็นโรคมะเร็งของโพรงจมูกชนิด "sinonasal undifferentiated carcinoma (SNUC)" และได้มารับการรักษาที่โรงพยาบาลจุฬาลงกรณ์ ผู้ป่วยรายนี้มีเนื้องอกที่เรียกว่า "inverted pailloma" ซึ่งเป็นเนื้องอกชนิด benign ของโพรงจมูกเกิดร่วมด้วย ลักษณะทางพยาธิวิทยาของ SNUC ประกอบด้วยเซลล์ตัวใหญ่ขนาดปานกลางจัดเรียงตัวเป็น nest หรือ sheets เซลล์มีการแบ่งตัวสูงรวมทั้งพบหย่อมเนื้อตายบ่อย สามารถพบบริเวณที่มี inverted papilloma ซึ่งเซลล์มีการเปลี่ยนแปลงกลายเป็นเซลล์ผิดปกติ (dysplasia) ผู้ป่วยได้รับการรักษาโดยวิธีรังสีบำบัดและเคมีบำบัด จากการติดตามผลการรักษาเป็นเวลาห้าเดือน ผู้ป่วยยังมีชีวิตและตรวจไม่พบรอยโรคหลงเหลือ มะเร็งชนิดนี้ได้รับการจัดแยกออกเป็นโรคพิเศษที่จำเพาะโรคหนึ่งเมื่อปีพ.ศ. 2529 ธรรมชาติของโรคมีความร้ายแรงมาก ผู้ป่วยมักจะเสียชีวิตภายในหนึ่งปีหลังจากได้รับการวินิจฉัย ลักษณะทางพยาธิวิทยาของมะเร็งชนิดนี้อาจแบ่งได้หลัก ๆ เป็นสองกลุ่ม คือ 1. Western type SNUC และ 2. Nasopharyngeal cell type เนื้องอกในกลุ่มหลังนี้ เกือบทั้งหมดพบในคนเชื้อชาติเอเชียและมีความสัมพันธ์กับเชื้อไวรัส EBV สูงกว่าในกลุ่มแรก ผู้ป่วยที่เป็นมะเร็งชนิดนี้ควรได้รับการรักษาอย่างเต็มที่ด้วยวิธีการหลายชนิดผสมผสานกัน จากการสืบค้นของผู้เขียน ยังไม่พบรายงาน sinonasal undifferentiated carcinoma ที่เกิดขึ้นในผู้ป่วยที่เป็น inverted papilloma มาก่อน

Sinonasal undifferentiated carcinoma (SNUC) is a distinct, relatively rare and aggressive neoplasm that arises in the nasal cavity and paranasal sinuses. Having reviewed of literature and recorded files of the Department of Pathology, King Chulalongkorn Memorial Hospital, no case of SNUC in Thai population has ever been documented. We believe that the rarity of the tumor report might be partly due to inability of pathologists or clinicians to recognize the entity of the tumor. To understand the rare prevalence of SNUC and its distinct clinicopathological features, we present a case of a 50-year-old Thai male who suffered from SNUC arising in pre-existing inverted papilloma.

Case report

A 50-year-old male presented with an asymptomatic left nasal mass for seven years. Left nasal obstruction had been earlier detected for two years; and left nasal bleeding had been noted for two months. On physical examination, the left nasal cavity was found to be occluded with a well-defined mass that extended from the superior to the inferior turbinates. Computed tomography (CT) of paranasal sinuses demonstrated a 1.5 x 4.5 cm left nasal mass at the middle meatus without bone erosion or sclerosis (Fig 1 and 2). Subsequently, the differential diagnosis included inverted papilloma, lymphoma, squamous cells carcinoma and some minor salivary gland tumors.

A biopsy was performed, and it showed acanthotic squamous epithelium with focal areas of inverted growth pattern. Inverted papilloma was suggested. The patient underwent left inferomedial maxillectomy.

Gross specimen showed multiple pieces of gray brown tissue with its greatest dimension of 4.5 cm.

Microscopic examination revealed medium-sized neoplastic cells that arranged in nests and sheets with numerous mitosis and massive necrosis (Fig 3 and 4). The nuclear/cytoplasmic ratio was high. Nuclei were round to oval with mild to moderate pleomorphic and hyperchromatic appearances containing slightly prominent nucleoli. The chromatin

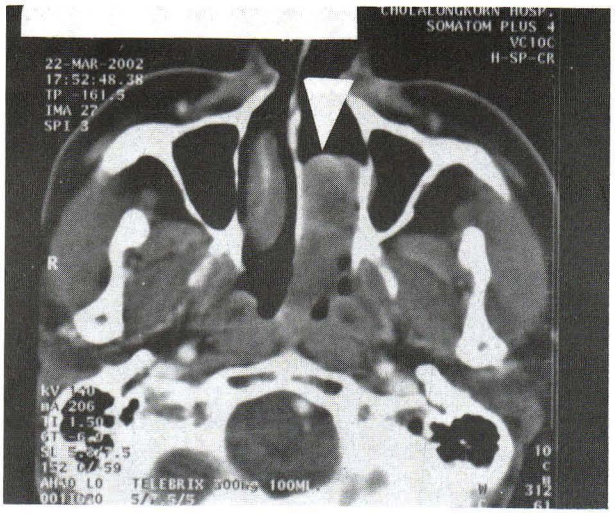

Figure 1. Axial CT scan post contrast study at the level of nasopharynx shows enhancing soft tissue mass (arrow) occupying the posterior part of left nasal cavity.

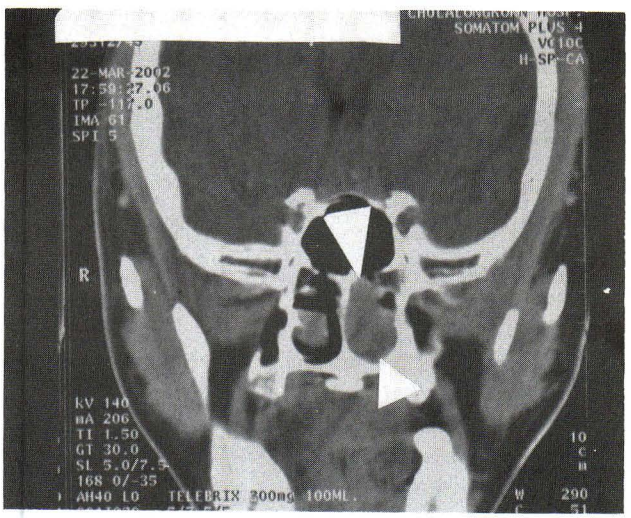

Figure 2. Post contrast coronal CT scan through the anterior part of sphenoid sinus shows a soft tissue mass (arrowed) occupying in the entire left nasal cavity.

distribution varied from coarsely granular to homogeneous and diffused pattern. They contained small to moderate amount of eosinophilic cytoplasms.Cell borders were distinct. Scant intervening stroma was observed. Dysplasia of the surface epithelium was noted focally. Inverted papilloma with areas of malignant change was obviously detected (Fig 5 and 6). The tumor cells were diffusely positive for keratin and negative for chromogranin and synaptophysin. Latent membrane protein 1 (LMP1) for Ebstein-Barr Virus (EBV) yielded negative result.

The final diagnosis was sinonasal undifferentiated carcinoma arising in preexisting inverted papilloma.The patient underwent radiotherapy and chemotherapy. On the last follow-up, 5 months after the initial treatment, there was no evidence of disease detected.

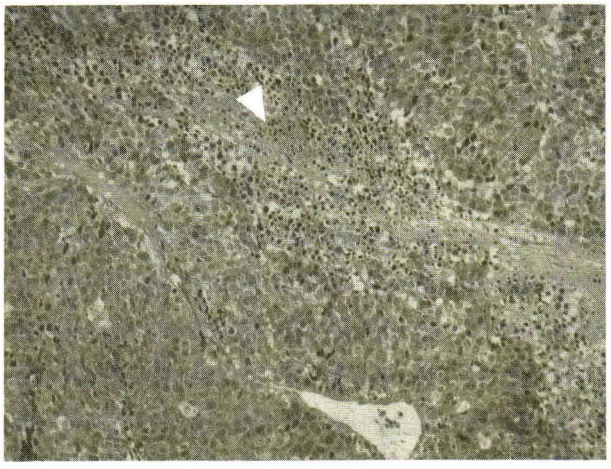

Figure 3. The tumor cells are arranged in sheets with foci of massive necrosis (arrowed).

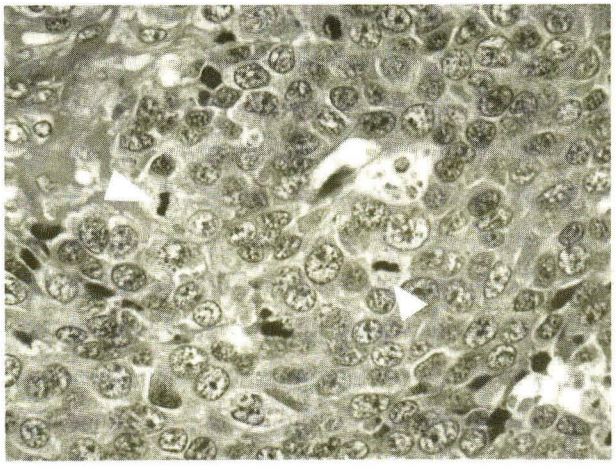

Figure 4. High magnification shows high mitotic figures (arrowed).

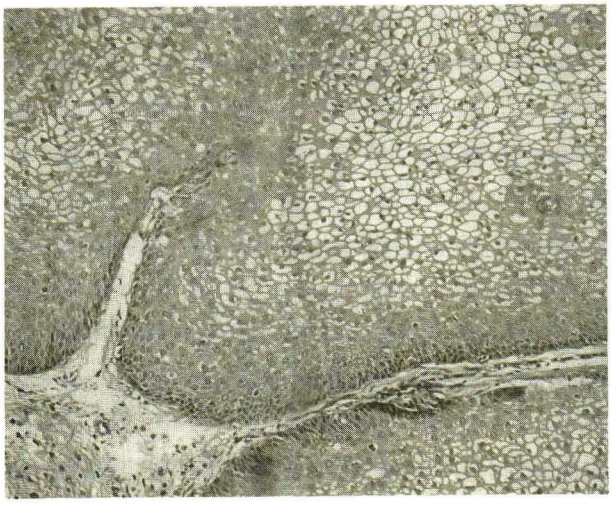

Figure 5. This area shows inverted papilloma.

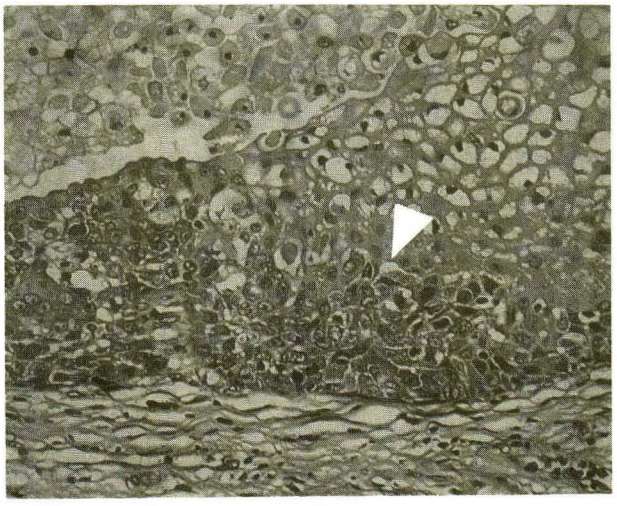

Figure 6. High magnification in some areas of inverted papilloma shows dysplastic changes (arrow).

Discussion

Sinonasal undifferentiated carcinoma is a rare but increasingly recognized neoplasm.[1] The tumor has been proposed as a distinct clinicopathological entity since 1986 by Frierson et al.[2] In the past, these lesions were frequently diagnosed as poorly differentiated squamous cell carcinoma[1] and were treated as such.

Recognition of this tumor as a distinctive entity is necessary because the neoplasms are clinically and pathologically different from squamous cell carcinoma. SNUC behaves aggressively and results in death within short period of time, mostly within 1 year after the diagnosis. [3,4]

The diagnosis of SNUC can usually be made by light microscopy alone.[3] Sometimes, however, immunohistochemistry is needed to distinguish them from other neoplasms that have some degree of histological similarities such as melanoma, malignant lymphoma and olfactory neuroblastoma.[3]

According to Lopategui et al.,[5] SNUCs were subdivided into three morphological categories: 1) "Western-type" SNUC (SNUC-WT), a subtype that has the morphologic appearances previously described by Frierson et al; [2] the neoplasms of this type consist of medium-sized polygonal cells with discernible cell borders and a small to moderate amount of eosinophilic cytoplasm. They are arranged in nests, trabeculae, ribbons and sheets. The nuclei are mildly to moderately pleomorphic and hyperchromatic and contain small and occasionally prominent nucleoli. Mitotic figures are numerous, and necrosis is extensive.[5] Morphologically, our case is best categorized into this type. 2) a subtype with morphologic features similar to anaplastic large-cell carcinoma of lung and other sites (SNUC-LC). and 3) a subtype that mimic nasopharyngeal undifferentiated carcinoma (SNUC-NP). Of the total 22 patients in that study, all 11 Caucasian patients had SNUC-WT while the 11 Asian patients had a broad histological spectrum (SNUC-WT, 3 cases, SNUC-LC, 3 cases and SNUC-NP, 5 cases).

Immunohistochemical studies of these tumors have shown that cytokeratin are positive in 88 -100 % of cases and epithelial membrane antigen are positive in 63 - 92 %. [7] About 23 - 50 percent of the lesions are positive for neuron-specific enolase.[7] Synaptophysin and chromogranin are negative in most studies but cases which stain positively for these two antibodies have been documented. [1,4,7] In such cases, however, the staining is usually weak to moderate and appears in limited areas.[4] Ultrastructurally, neurosecretory-type granules are seen in some cases.[1,2] In our opinion, cases which express such neuroendocrine features should be regarded as neuroendocrine carcinoma in stead of SNUC.

The tumor that is most often confused with SNUC is olfactory neuroblastoma (ONB).[2] Olfactory neuroblastoma has a much better prognosis than SNUC, therefore, should be distinguished from the latter.[1] Cytologically, ONB exhibits less degree of necrosis, mitotic activity, nuclear pleomorphism, or tendency for angiolymphatic invasion when compared to SNUC.[7] Fibrillary cytoplasmic background typically present in ONB is another helpful differentiating feature.[1] Comparison between these two neoplasms is illustrated in table 1.

To distinguish SNUC from poorly differentiated squamous cell carcinoma, one should focus on the presence or absence of squamous differentiation.

Table 1. Comparison of clinical and pathologic features for olfactory neuroblastoma (ONB) and sinonasal undifferentiated carcinoma (SNUC).

Feature	ONB	SNUC
Clinical		
Site	Roof of nasal cavity	Multiple sites
Prognosis	60 – 80 % 5 yrs.	Less than 1 yr
Ocular-cranial nerve	Occasional	Common
Symptoms		
Pathological		
Growth pattern	Lobular	Nests, trabecular, ribbon, sheet
Nuclear features	Uniform, Occasional pleomorphic	Anaplastic
Mitoses	Variable	Numerous
Necrosis	Occasional	Prominent
Neurofibrillary	Common	Absent
Stroma		
HW rosettes	Common	Absent
Keratin	25 – 35 %	90 %
S-100	60 %	0 – 15 %
Synaptophysin	64 –100 %	0 %
Neurosecretory granules	Numerous	Rare

Modified from Frierson HF Jr. et al: Am J Surg Pathol 10: 771-779, 1986 and Kapadia SB. Tumors of the Nervous System. In: Barnes L.(ed). Surgical Pathology of the Head and Neck, 2nd ed. New York: Marcel Dekker, Inc. 2001: 844

Accordingly, SNUC should not exhibit squamous or glandular differentiation.[2] If such features are detected, poorly differentiated squamous cell carcinoma or adenocarcinoma should be considered.

Melanomas arising in the sinonasal region can be distinguished from SNUC if pigmentation is detected. [2] For cases that lack pigments, the diagnosis is based on immunohistochemical studies (S -100 protein and HMB-45)[2,6] (see table 2). In addition, prominent eosinophilic nucleoli and thegue-like growth pattern as well as junctional melanocytic change are features suggestive of melanoma.[2]

Prior to the advent of immunohistochemistry, SNUC and malignant lymphoma were frequently misdiagnosed in both directions since the former may closely mimic large cell lymphoma. [1] With availability of immunohistochemical studies, distinction between these two entities is straightforward. Malignant lymphoma stains strongly for leukocyte common antigen while SNUC typically shows diffused positivity for cytokeratin[1] (see table 2).

Table 2. Immunohistochemical staining for differential diagnosis of SNUC.

Tumor	CK	LCA	Synaptophysin	HMB-45
SNUC	+	-	-	-
ONB	+/-	-	+	-
ML	-	+	-	-
MM	-	-	-	+
NEC	+	-	+	-

SNUC = Sinonasal undifferentiated carcinoma; ONB = Olfactory neuroblastoma; ML= Malignant lymphoma; MM = Malignant melanoma: NEC = Neuroendocrine carcinoma Modified from Barnes et al. Surgical Pathology of the Head and Neck, 2nd ed. New York: Marcel Dekker, Inc, 2001: 512 and Mills SE et al. Atlas of tumor pathology, 3rd series, fascicles 26. Washington D.C. Armed Forces Institute of Pathology, 1997:167-180

Since SNUC-NP morphologically resembles undifferentiated carcinoma of the nasopharynx, although the latter has more lymphoid stroma, knowing the location of the lesions is necessary for arriving at the correct diagnosis. The distinction between SNUC-WT and NPC is based on morphological characters of each tumor. NPC is composed of cells with vesicular nuclei which grow in syncytial-like sheets.[1] Mitoses and necrosis are not prominent.[7] SNUC-WT consists of nests, trabeculae, ribbons and sheets of medium-sized polygonal cells with hyperchromatic nuclei.[1] The cell borders are distinctive. Mitotic figures are numerous; and necrosis is extensive.[1] (see table 3).

Clinically, SNUC affects variable age of the patients, but the mean age is about 50 - 60 years with the range of 20-85 years.[7] When all series are collectively reviewed, there is no significant gender preference detected.[7] In the series of Yung-Ming Jeng et al.,[4] SNUC with the features of SNUC-WT had the median age of occurrence at 53 years (range 20 -76 years), with male/female ratio of approximately 2:1. However, the median age of nasopharyngeal-type undifferentiated carcinoma, was slightly higher (58 years with the range of 36 - 75 years), with the same male/female ratio of approximately 2:1. The clinical symptoms of the tumor are nonspecific, i.e., enlarged sinonasal mass, nasal obstruction, recurrent epistaxis, anosmia, proptosis, periorbital swelling, decreased vision, facial pain and occipital headache, etc.[1, 6] The common sites of involvement are, namely: nasal cavity, maxillary and ethmoid sinuses.[1,8] Intracranial and orbital involvements are also common.[1,8]

SNUC is a destructive and very lethal disease. Although a few individuals have managed to survive longer than 5 years, most patients died within 1 year after the diagnosis.[7] The tumors have high rate of local recurrence with frequent regional and distant metastasis. From 16 cases with available follow-up data in the series of Cerilli et al,[8] the local recurrence was found 56 %; and 75 % developed metastatic disease, most of which were extensive. Cervical node involvement was detected in 50 % of cases. The subtype

Table 3. Comparison in clinicopathologic features of Sinonasal Undifferentiated Carcinoma, Western type (SNUC - WT), Sinonasal Undifferentiated Carcinoma, Nasopharyngeal typ e (SNUC - NP) and Undifferentiated Nasopharyngeal Carcinoma (UNPC).

Features	SNUC-WT	SNUC-NP	UNPC
Race	Both Asian and Caucasian	Asian	Common in Asian, rare in Caucasian
Location	Sinonasal tract	Sinonasal tract	Nasopharynx
Growth pattern	Nests, trabecular, ribbons, Sheets	Cohesive nests or sheets	Ill-defined sheets
Cells	Medium-sized, polygonal-shaped with hyperchromatic nuclei	Large vesicular nuclei with prominent nucleoli	Large, vesicular nuclei with prominent nucleoli
Cell borders	Distinct	Indistinct (syncytial)	Indistinct (syncytial)
Necrosis	Common	Uncommon	Uncommon
Mitoses	Very prominent	Very prominent	Not prominent
Lymphocytes	Mild	Mild to moderate	Heavy infiltrate
EBV	Rare	Common	Common

Modified from Jeng YM et al. Am J Surg Pathol 26 (3): 371-6, 2002, Lopategui JR et al. Am J Surg Pathol 18(4): 391-8, 1994 and Barnes et al. Surgical Pathology of the Head and Neck. New York; Marcel Dekker, Inc, 2001: 509-32

with such aggressive behavior usually refers to SNUC-WT. The natural history of SNUC-NP subtype has not been well established because of inadequate follow-up data due to limited cases reported in the literature (fewer than 40).[4]

The optimal treatment of SNUC has not yet been established. Surgical resection, radiation or chemotherapy have been of no curative value.[1] In the study of Musy et al.,[9] it seems that chemoradiotherapy followed by craniofacial resection (CFR) might give a better outcome than palliative radiotherapy or chemoradiotherapy alone. Two-year survival was 64% in the group treated by CFR and 25 % in the group treated with chemotherapy and/or radiotherapy. The difference, however, was not statistically significant (P = 0.076). It is recommended that SNUC should be treated aggressively by multimodal approach.[10,11] In the case, the patient was treated with radiotherapy 6,000 cGy in 30 fractions and 6 cycles of chemotherapy (Carboplastin / vp-16) showed satisfactory response. To determine a long-term outcome, however, longer period of follow-up is necessary.

Etiologies of the tumor still remain unclear. Association with cigarette smoking was suggested by some studies. [2,12] The role of Epstein-Barr virus (EBV) in the development of SNUC has been investigated by several groups [4,5,8,12] in which they gave variable results. EBV has been reported to present in both

SNUC and nasopharyngeal-type undifferentiated carcinoma. [4,5,12] However, nasopharyngeal-type SNUC (SNUC-NP) show stronger association with the virus compared to the western type. [4,5] Since LMP-1 immunostaning is not as sensitive as Insitu Hybridization studies for detection of the EBV, [5] therefore negative result in this case could not rule out EBV infection.

Because of the differences in the relation with EBV, morphology and probably prognosis between SNUC and Nasopharyngeal-type undifferentiated carcinoma, it was suggested that these two tumors should be considered as two entirely different entities. [4] Whether the biologic behavior of each tumor is different or not is yet to be determined.

The incidence of malignant change in inverted papilloma ranged from 2 to 27 % in different series (average 14 %). [7] The types of carcinoma documented to complicate such lesion include squamous cell carcinoma, verrucous carcinoma, mucopidermoid carcinoma, spindle cell carcinoma, clear cell carcinoma, transitional carcinoma as well as adenocarcinoma. [7,13] To the best of our knowledge, this is a first example of inverted papilloma associated with SNUC

Of all carcinoma associated with inverted papilloma, approximately 61% are synchronous and 39 % metachronous. For metachronous carcinoma, the mean interval between onset of the inverted papilloma and the development of carcinoma is about 63 month (range 6 month -13 years). [14] Since the duration of symptoms in this patient was quite long, it is possible that the lesion was benign at the beginning and SNUC developed later in the course of diseases.

In summary, the authors would like to stress that Sinonasal undifferentiated carcinoma is a distinctive and highly aggressive neoplasm which should be recognized by clinicians and pathologists in order to be aware of its biological behavior and in order to give an appropriate treatment.

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