Intracranially Extended Sinonasal Undifferentiated Carcinoma: A Case Report and Literature Review

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Patient: Male, 41-year-old
Final Diagnosis: Sinonasal undifferentiated carcinoma
Symptoms: Nasal congestion
Medication: —
Clinical Procedure: Craniotomy
Specialty: Neurosurgery

Objective: Unusual clinical course
Background: Sinonasal undifferentiated carcinomas (SNUC) are highly malignant and rare lesions. Therapeutic efforts often provide frustrating results. Their course is characterized by indolent progression, until it culminates in extensive local infiltration of adjacent anatomical structures or cervical lymphadenopathy in approximately one-third of patients upon admission. It most frequently affects males, with a sex ratio of 3: 1. The age at manifestation tends to be about 40-50 years.

Case Report: We report the case of a 41-year-old man with intracranial expansion of SNUC. Two previous sinus surgeries were performed endoscopically because the lesion at that moment was exclusively located endonasally. Within the last few months, he had been having persistent headaches. Magnetic resonance imaging (MRI) revealed an anterior cranial fossa lesion. Therefore, he underwent a bifrontal craniotomy and excision of the space-occupying lesion (SOL). The osseous defect of the skull base was covered with a titanium mesh. Finally, we performed a duraplasty using a pericranial flap and fat tissue taken from his abdomen. Postoperatively, his wound was dehisced. We proceeded then to a frontal craniectomy with surgical debridement, subgaleal empyem and epidural abscess removal, and copious irrigation with oxygen peroxide. Enterococcus spp. were isolated from pus cultures. Despite receiving bacteria-focused antibiotics, he unfortunately developed sepsis and died. The histopathologic findings revealed a SNUC, which is the criterion standard for diagnosis.

Conclusions: Multimodal treatment offers the best prognosis to patients with SNUC. Combined operations by otolaryngologists and neurosurgeons provide the necessary radicality. There is high risk of wound healing disorders, especially when local irradiation had been administered.

Keywords: Epidural Abscess • Sepsis • Sinonasal Undifferentiated Carcinoma

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Background

Undifferentiated carcinoma of nasal sinuses constitutes a very rare and malignant tumor that is often frustrating to treat [1]. It progresses indolently, until it develops extensive local infiltration of proximal structures [2] or with cervical lymphadenopathy in 10-30% of patients upon admission [3]. The initial clinical signs usually show benign manifestation, such as nasal congestion, headache, nose-bleed, or facialgia; visual deficits, periorbital edema, exophthalmos, and cranial nerve paralysis may also appear [4]. There is documented to be more common in males, with a 3: 1 sex ratio. They usually appear in patients in their forties, ranging from age 8 to 85 years [4]. When these carcinomas are diagnosed they are usually associated with progressive deterioration and general poor prognosis [5].

Here, we report the case of a 41-year-old man with intracranial expansion of sinus nasal undifferentiated carcinoma (SNUC). Two endoscopically performed sinus surgeries were performed and the lesion was exclusively located endonasally.

Case Report

A 41-year-old man was admitted to our Neurosurgical Clinic owing to refractory frontally located headaches within the last 7 days, and he had vomiting and nuchal pain. His past medical history at an ear-nose-throat (ENT) clinic included a Draf IIa frontal sinusotomy 6 months before, where a SNUC lesion was removed. The malignancy was located at an adjacent nasoethmoid site and there was no lymphadenopathy or metastases (T2N0M0).

Owing to local recurrence and bony erosion of the cribiform plate without intracranial extension, he underwent a Draf IIb procedure 2 months afterwards. Duraplasty and endonasal flap mobilization was performed due to cerebrospinal fluid (CSF) leakage.

During the last hospitalization he also had an acute coronary incident that necessitated emergent coronography and stenting. He had also received 3 cycles of cisplatin combined with 60 Grays (Gy) of intensity modulated radiotherapy (IMRT) over a 6-week period.

During the present admission, the initial radiologic control with head computed tomography (CT) revealed a hyperdense anterior cranial fossa space-occupying lesion (SOL) on his left side (Figure 1A, 1B). The SOL was abutting the ethmoidal and frontal bones and eroded inner orbital wall and had perifocal edema. We stopped his antithrombotic treatment for 1 week and then performed magnetic resonance imaging (MRI). The tumor had high intensity on T1 images and was enhancing after contrast medium administration. On T2 sequences, it was isointense and its dimensions were 1.7×2 cm. It was infiltrating the dura propria of the left frontobasis and left orbital gyri. Vasogenic edema was present on fluid-attenuated inversion recovery (FLAIR) sequences, extending to the left frontal lobe up to the ipsilateral frontal ventricular horn. Therefore,
we proceeded to the third operation (Figure 2A-2E). He un-
derwent a bifrontal craniotomy with excision of the SOL via an intradural plane. The osseous defect of the skull base was covered with titanium mesh. We also performed a duraplas-
ty using a pericranium flap and a fat graft taken from the ab-
domen (Figure 3).

Ten days after the operation, he had fever and pus egression from the wound region, but his neurological status was intact. The new CT showed subgaleal empyem and epidural abscess in the surgical area (Figure 4). We proceeded to a frontal craniecto-
my with surgical debridement, removal of osseous flaps, and co-
pious irrigation with oxygen peroxide. Two retractable duplicated sheets of iodoform gauze were left as drainage frontal-bilaterally.

In pus cultures, we isolated *Enterococcus* spp. Despite receiv-
ing bacteria-focused antibiotics, he developed sepsis and died.

The histological examination of the samples revealed medi-
um-size cuboidal cells, with round and oval nuclei with nucle-
oli, a high nuclear/cytoplasmic ratio, moderate to increased pleomorphism and atypia, and increased mitotic activity. They are densely arranged with extended necrosis. Glial cells were with GFAP stain and were located at the margin of the tumor specimen. Immunohistochemical stains were performed. All the neoplastic cells were strongly positive for keratins CK7 and CK8/18 (Figure 5). Due to the morphology of the neoplastic cells and according to the current immunophenotype, our di-
agnosis was compatible with SNUC.
Discussion

SNUC arises from the olfactory epithelium of the sinonasal mucous membrane and shows abnormal intermediate-sized cells forming nodules or lamellae with necrosis, vascular permeation, and mitoses [6]. SNUC potential malignancies for these structures are carcinomas of the squamous layer, neuroepithelial carcinoma, carcinoid, malignancies of lymphatic tissue, melanocytes and skeletal muscle cancer, and lymphoepithelioma [1]. Histopathology and immunohistochemical assessment are the criterion standard for diagnosis [7].
Rosenthal et al [8] estimated the overall rate of newly diagnosed cases at 0.00002% and the 5-year OS rate at 35%, which is worse than for neuroendocrine sinonasal tumors. Older age at diagnosis is associated with shorter survival. The cut-off age with worsening prognosis was 60 years. Patients older than 70 years showed 2.5 times higher mortality rate [8]. Cervical metastases, distant dissemination, lesions with mostly undifferentiated cells, and subtotal resection are associated with worse prognosis [9]. Kadish [10] introduced a new scale to assess the extension of SNUC; Kadish stage C corresponds to infiltration of the orbit, skull base, or cerebral parenchyma [11].

Immunohistochemically, it is positive for cytokeratin, mixed positive/negative for epithelial membrane antigen (EMA) or neuron-specific enolase, and negative for S-100 protein [1].

In poorly undifferentiated carcinomas, deletion of SMARCB1 and SMARCA4 genes at the SWI/SNF complex has been proposed to constitute a pathognomonic marker of these neoplasms [12].

Amigay et al [13] studied 10 SNUC specimens and all tumors had complete deletion of the tumor suppressor gene SMARC4 and limited expression of SMARCB1/INI1, and all tumors had the classic positive pankeratin stain in immunohistochemistry. In their most recent studies, they focused on the detection

Figure 5. (A) H-E x100 Cuboidal cells with increased nuclear-cytoplasmic ratio. (B) H-E x400A Round and oval nuclei with nucleoli and moderate to increased pleomorphism and atypia. (C1) H-E x100 densely arranged neoplastic cell with extended necrosis. (C2) GFAP x400 glial cells lie at the margin of tumor specimen. (D1). CK7 x100 cells positive in CK7 stain. (D2) CK 8/18 x200 cells positive in CK8/18 stain.
of IDH2 mutations as the common feature of the group [14].
These facts indicate that these neoplasms are a rather homo-
genous group, which warrant a tailored approach.

A case series by Miyamoto et al [15] found survival over 5
years despite tumors advancing intra-cranially/orbitally. This
suggested that extension itself had no effect on survival and
that long-term survival was better with aggressive treatment.

Chambers et al [16] reported that resection alone had an overall
advantageous effect on prognosis, with an HR of 0.73 (95% CI,
0.52-1.02). On the other hand, Kim and associates [17] report-
ed a series of 8 patients treated within a period of 10 years,
who had not received combined therapy. Consequently, they
had poor outcome at 12-month follow-up, and only 2 out of
8 patients were alive and tumor-free.

Radiation alone showed a relative overall survival advan-
tage [18]. Thus, approaches employing a schema of resec-
tion, irradiation, and chemotherapy are the mainstay of SNUC
treatment [3,19].

Regarding the utility of chemotherapy, it seems that SNUC
responds well to it both before and after surgery or irradiation
[3,18]. Tumors with undifferentiated cells may not have
such an adverse cell proliferation and thus tend to respond
better to such treatment [3]. Chemotherapy can also reduce
a lesion’s apposition in regions proximal to regions with crit-
ically low radiation threshold (eg, optic nerves), thus improv-
ing the outcomes [3,20].

A meta-analysis by Morand et al [21] found that SNUC ap-
peared to be a chemosensitive tumor presenting most com-
monly to males and that surgery alone was not as effective
as combined treatment. They estimated the 2-year local re-
currence rate was 27% and 16% of patients had metastatic
lymphadenopathy [21].

Regimens of either cyclophosphamide,vincristine and doxo-
rubicin, or etoposide and cisplatin are usually administered.
The 2- and 5-year OS rates were 47-65% and 37-43%, respec-
tively [22].

Concerning irradiation, no strict guidelines exist. Christopherson
et al [23] treated 23 patients with doses greater than 62.4 Gy
and reported cause-specific survival. Doses varying from 50
to 65 Gy are now recommended due to a probable dose-re-
sponse relationship. This result may also encourage the use of
IMRT, which allows higher doses and avoids negative effects,
such as retinopathy [24].

Gorelick et al [25] published a case series of 4 patients treated
multimodally with chemotherapy, radiotherapy, and aggressive
skull base surgery to the anterior cranial fossa. Three of the 4
patients died due to their disease approximately 15 months
after diagnosis. The 1 survivor developed intracranial disease
2 years after diagnosis.

Orlandi et al [22] stated that a multimodal treatment strategy
with induction chemotherapy provides longer overall survival
(OS) and when there was recurrence, early surgery offered a
survival benefit compared to stand-alone chemotherapy [22].

Xu et al [4] published a meta-analysis of 160 patients, of whom
only 20 were treated by them. The survival rates at 1, 3, and 5
years were 51.2%, 19.45, and 6.25%, respectively [4]. The pe-
riod of time within at least half of the patients had survived
was only 12.7 months. Only 39% of the patients underwent
combined treatment with surgery and either chemotherapy
or radiotherapy. Using Cox regression analysis, Xu et al [4]
found a prognosis benefit related to combined therapeutic
methods (P=0.015).

Reiersen et al [2] aggregated 167 cases to provide robust evi-
dence favoring multimodality treatment. Patients receiving
combined treatment had increased chances of survival, rat-
ing 260%, compared to stand-alone surgery.

Chambers et al [16] reported that surgery, irradiation, and
chemotherapy combined provide prognostic benefits in cas-
es of disease progression, compared use of a single method
(P=0.015, <0.01, and <0.01, respectively).

Optimized surgical techniques incorporating craniofacial ap-
proaches [8] and endoscope application to the skull base ar-
eas [19] have contributed significantly to this evolution over
the last 40 years [16]. Radiosurgery to the skull base may fur-
ther improve survival, especially when total resection is not
feasible [18].

As far as the type of surgery is concerned, Hanna et al [26] had
conducted a retrospective study concerning 120 patients with
sinonasal malignancies. They concluded that an endoscopic
approach combined with craniotomy enables larger dura ex-
cision and better vascularization in the meningeal flap before
high-dose radiation therapy [26]. They also found that disease
recurrence and OS were not significantly different between
use of endoscopic resection alone versus endoscopic resec-
tion plus craniotomy [26].

Donald et al [27] described a series of 13 patients with skull
base erosion, the majority of whom had extensive intra-cal-
varial and extracranial dissemination. No distant or cervical me-
tastases had been reported upon presentation. The majority of
the patients had undergone classical lateral rhinotomies, an-
terior maxillary ostectomies, or a medial maxillectomy along
with a low anterior craniotomy. Seven patients died within 20 months after treatment. Survival at 2 years and beyond was 57%. Their tactic was intracranial/extracranial resection and postoperative irradiation, which they also advocate in their conclusions [27]. Twenty months is considered the critical time after which multimodal treatment is considered successful [27].

Pradeep et al [28] published a case report of a male patient with an extra-axial lesion emerging from the ethmoidal sinus and intracranial extension into the frontal lobes with perifocal edema. The patient had left anosmia and anosmia. They excluded the presence of abdomen and thorax metastases with ultrasound (USG) of the abdomen and chest X-ray, and performed bifrontal craniotomy and fronto-orbital osteotomy with gross total resection of the lesion. The frontal sinus was cranialized and a pericranial flap was used as sealant. Bone reconstruction was performed with titanium plates and screws. At 1-year follow-up, the patient was alive.

Prasad et al [29] reported a 43-year-old man with bifrontal headache and nasal obstruction within the last 3 months. He was neurologically intact. In radiological examination, SOL was depicted in frontobasal and ethmoidal region and was attached to the medial wall of the left orbit. A tumor and its osseous apposition surfaces were removed. The frontal sinus was cranialized and the dura was repaired. The patient developed ipsilateral impairment of all cranial conjugates within the first week in the context of Garcin syndrome.

Hofer et al [30] presented a 62-year-old woman with nasal constipation on the right side and anosmia. Physical examination revealed a glazed, hemorrhagic SOL of her right nasal cavity and right nasopharynx extending contralaterally. Radiologic examination showed a tumor arising in the right sinus eroding the right lamina cribrosa and the posterior wall of the right frontal sinus. The tumor was near the frontal lobe, olfactory and optic nerves and infiltrated the meninges. After obtaining a specimen that confirmed the diagnosis, the patient was operated on both transnasally and via open craniotomy.

Yeung et al [31] retrospectively evaluated 17 patients who had local sinonasal malignancy progression. All patients were previously operated on and had also received chemotherapy and radiotherapy. The authors reported that they had achieved complete resection and the median progression-free survival was 24 months, whereas the median OS was 60 months. They found that salvage surgery was also an effective treatment.

Surgeons who strive to achieve radicality should consider the physiological dysfunction of the nasal cavity in malignancies. First of all, mucociliary clearance is impeded. In chronic inflammation states such as chronic rhinosinusitis, this phenomenon has been widely studied and is reported to reduce ciliary beat frequency and alterations in mucosal viscosity. Ciliary frequency is related to many factors like temperature, hormones, pH alterations, stress, and neurotransmitters. Mechanical factors such as pressure exerted on the cilia also induce their motility [32]. In addition, plasma exudation and its flow across epithelial cells constitute a second protective mechanism that not only mechanically removes pathogens, but also contains immunoglobulins. Its production is attributed to the cyclic obstruction and decongestion of the nasal venous capillaries [33]. Presumably, this procedure is also less effective in case of malignancies.

Yin et al [34] evaluated the mucociliary transport rate of 66 patients who had undergone IMRT over a period of 12 months. Utilizing multiple regression analysis, they found that the nasal radiation dose was an independent factor impairing mucociliary function, and they determined the tolerance threshold of radiation as 37 Gy [34].

Radical resections, on the other hand, reducing inferior turbinate mucosa, lead to decreased heating and humidification of the nasal cavity and thus share an increased risk of massive nasal desiccated discharge. Therefore, extension of the nasal airway and sinuses should be avoided [35].

Consequently, the consistency of the upper respiratory microbiome may alter after radiotherapy [36] and FESS procedures [37]. This fact combined with the distorted anatomy may result in serious infections and wound healing disorders.

Conclusions

Multimodal treatment is the standard of medical care for SNUC and provide prognostic benefits. Joined skull base procedures from both ENT and neurosurgeons achieve the necessary radicality, especially in cases of intracranial extension. However, refractory postoperative infections and wound healing disorders should be expected as a result of this therapeutic approach.

Statement

Patient was treated in 1st Academic Neurosurgery Department, Aristotle University of Thessaloniki, AHEPA Hospital, Greece.

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