**Sinonasal undifferentiated carcinoma – a case report**

**Niezróżnicowany rak zatokowo-nosowy – Sinonasal undifferentiated carcinoma (SNUC) – opis przypadku**

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**ABSTRACT:**

**Introduction:** Neoplasms of the nasal cavities and paranasal sinuses always require urgent diagnostics tests to determine their malignancy and plan of the treatment. Both benign and malignant tumours have initially similar, unilateral symptoms – nasal obstruction, bleeding, runny nose. Malignant neoplasms of the nasal cavities and paranasal sinuses are characterized by aggressive growth, fast infiltration of the surrounding structures (including the orbit and skull base) and metastasize to the regional lymph nodes. The prognosis of the patient’s survival the best improves the early diagnosis.

**Case report:** In our case report, the unilateral lacrimation was not properly interpreted as a first tumour symptom. A dacryocystorhinostomy was performed without prior diagnostic imaging, which significantly delayed the diagnosis.

**KEYWORDS:** case report, nasal cavity, paranasal sinuses, sinonasal undifferentiated carcinoma

**STRESZCZENIE:**

**Wprowadzenie:** Nowotwory jam nosa i zatok przynosowych zawsze wymagają pilnej diagnostyki celem określenia ich charakteru i zaplanowania leczenia. Zarówno nowotwory łagodne, jak i złośliwe początkowo objawiają się podobnie – niedrożnością nosa, krwawieniem, wyciekiem z nosa (zwykle jednostronnym). Nowotwory złośliwe tej okolicy charakteryzują się zwykle agresywnym wzrostem, szybko powodują naciekanie okolicznych struktur (w tym oczodołu i podstawy czaszki) oraz przerzuty do regionalnych węzłów chłonnych. Największą szansę na przeżycie pacjenta daje wczesne rozpoznanie.

**Opis przypadku:** W opisanym przypadku wczesny objaw w postaci jednostronnego łzawienia nie został odpowiednio zinterpretowany. Wykonano dacryocystorhinostomię without prior diagnostic imaging, which significantly delayed the diagnosis.

**SŁOWA KLUCZOWE:** jama nosa, niezróżnicowany rak zatokowo-nosowy, opis przypadku, zatoki oboczne nosa

**ABBREVIATIONS**

AJCC – American Joint Committee on Cancer system
CK – cytokeratins
CT – computed tomography
DILO – Diagnostic and Oncologic Treatment
EMA – epithelial membrane antigen
ENT – ear, nose, throat
MRI – magnetic resonance
NSE – neuron-specific enolase
PET – positron emission tomography
SNUC – sinonasal undifferentiated carcinoma

**INTRODUCTION**

Malignant tumors of the nasal cavities and paranasal sinuses are rare. Primary tumors and metastases in this location constitute only 3% of all malignant tumors of the head and neck area [1, 2]. These are usually aggressively growing tumors, which due to the very late onset of symptoms are diagnosed at an advanced stage of the disease, hence are difficult to cure [3]. The most common malignant tumor of the nasal and sinus cavities is squamous cell carcinoma, accounting for approximately 40–55% of all malignant tumors of this region [2, 4]. Sinonasal undifferentiated carcinoma (SNUC) is a rare, aggressive, epithelial neoplasm of high malignancy and uncertain origin. The main and non-specific symptom is progressive nasal obstruction, which may occur in other more common nasal and sinus disorders. Diagnosis, in addition to the classic clinical examination, is based on imaging studies. The final diagnosis is established on the basis of histopathological examination, often supplemented with immunohistochemical staining. Because of the high aggressiveness of the tumor, combined treatment is implemented: surgery, chemotherapy and radiotherapy in various combinations. We report a case of a patient with late diagnosed undifferentiated sinonasal carcinoma, whose first symptom was unilateral epiphora of unknown cause.
CASE REPORT

A 59-year-old woman with no history of chronic disease was referred to hospital from an ENT clinic for right-sided facial swelling, eye tearing, obstruction of the right nasal cavity, and leakage of watery discharge. The patient had been observing isolated tearing on the right side for about 4 months, which over time was joined by swelling of the eyelids on the right side. She denied a previous history of chronic sinusitis, craniofacial trauma, and nasal and sinus surgery. Three weeks prior to the emergency room consultation, the patient had been scheduled for a right-sided transcanalicular laser bag-nasal anastomosis with Crawford probe tear duct intubation without prior diagnostic imaging as part of her private medical care.

According to the patient, after the procedure the operator diagnosed the presence of granuloma in the nasal cavity, but the tumor specimen was not taken for histopathological examination and further diagnostics was recommended in the ENT clinic. Due to the aggravation of symptoms after surgery, the patient was treated with clindamycin without improvement, and fivefold elevated c-reactive protein values were observed in blood tests. On physical examination in the emergency room, significant swelling of the face on the right side, swelling of the eyelid, and tearing of the right eye were noted. The patient denied visual disturbances, eye movements were symmetrical. Mucosal edema was evident in the right nasal cavity. Significantly enlarged inferior nasal auricle displaced the nasal septum to the left, completely obliterating the left nasal cavity, in which watery discharge was present.

An emergency room computed tomography (CT) scan of the sinuses was performed and described the presence of a huge abnormal mass measuring 41 x 50 x 50 mm filling the right maxillary sinus and right nasal cavity. The tumor protruded into the orbit through a defect in the orbital bone wall (approximately 24 x 26 mm), causing extensive bony destruction in all walls of the right maxillary sinus and penetrated into the soft tissues of the cheek. The orifices of the right frontal and wedge sinuses were found to be obstructed and partially filled by mucosal thickening and secretions.

The patient was admitted urgently to the Clinic with a DILO (Diagnostic and Oncologic Treatment) card. A specimen was taken from the right nasal cavity for histopathological examination, which proved to be non-diagnostic. Magnetic resonance (MRI) of the head with contrast was ordered, which described an abnormal mass in the right nasal cavity and maxillary sinus measuring 35 x 56 x 49 mm undergoing contrast enhancement, with bony destruction of the maxillary alveolar process, and infiltration of the soft tissues of the cheek. The tumor mass protruded into the oral cavity, entered the right orbit and displaced the eyeball and orbital muscles. The nasal septum was displaced to the left side with segmental destruction. No cervical lymph node enlargement was visualized.

The patient was admitted to the Department of Otolaryngology UCK WUM for biopsy from intranasal access under general anesthesia. After advancing the inferior nasal turbinates, the tumor mass was reduced. The pseudotumor sac (discontinuous) was identified, which allowed further preparation. A type 3 medial endoscopic maxillectomy was performed. A cavity was found in the anterior wall of the sinus. The lamina papyracea was destroyed by the tumor, but it was possible to dissect it from the almost unchanged orbital periorbita. The drain placed during dacryocystorhinostomy was removed. The part of the tumor attached to the lacrimal sac was resected. The floor of the nasal cavity was not infiltrated. The part of the tumor infiltrating the alveolar process and invading the infrathoracic fossa was left. After the procedure, the patient was observed to have normal ocular motility, preserved visual acuity, and no signs of bleeding. There were no evidently enlarged lymph nodes in the area examined up to the level of the larynx. Histopathological examination described the presence of numerous fragments of sinus mucosa with infiltration of carcinoma with a morphology that may correspond to sinonasal undifferentiated carcinoma (SNUC). In additional tests: CKAE1/E3(+) , CK7(+), CK5/6(+/-), p63(-), p40(-), EMA(-/+), NSE(-), synaptophysin(-), S100(-). Postoperative PET scan described a metabolically active infiltrate spreading along the walls of the right maxillary sinus, without lesions with features of distant metastasis. The patient was qualified for follow-up radiochemotherapy at the oncology consensus meeting.

At present, the patient is one and a half years after the initiation of cancer diagnosis, she has undergone 54 courses of radiotherapy and 2 courses of chemotherapy. Swelling of the right cheek and eyelids still persists, visual disturbances of the right eye have appeared. Unfortunately, follow-up imaging examinations after oncological treatment showed diffuse foci of bone metastases. The patient was qualified for palliative chemotherapy.

DISCUSSION

Undifferentiated sinonasal carcinoma is a rare epithelial malignancy of the nasal and sinus cavities, accounting for only 2% of all cancers of this region [2]. In Polish literature we can find only single articles devoted to this disease. Its final diagnosis is based on immunohistochemical examination. It does not have features of squamous or glandular differentiation. According to some authors, SNUC is a malignant neoplasm of neuroendocrine origin originating from the nose and sinuses, although on the other hand there is insufficient immunoreactivity characteristic of this type of tumor [5]. SNUC is more common in men (2–3: 1) on average between 50 and 60 years of age [5]. Symptoms appear suddenly and rapidly worsen and depend on the involvement of the primary tumor site, i.e., the nasal and sinus cavities: obstruction and nosebleeds, discharge, facial pain and headache. In case of orbital infiltration there are visual symptoms – exophthalmos, double vision, visual acuity disorders up to blindness. The time from onset of symptoms to diagnosis is about 4 months [6].

In the case we described, the first symptom was unilateral tearing of unknown cause, with no history of sinusitis, trauma or surgical treatment, which should suggest a neoplastic process. In such cases, a thorough nasal endoscopic examination should be performed, and urgent radiological diagnosis and biopsy are required if a tumor is present [7].

In the present case, biopsy was extended due to relatively favorable intraoperative conditions. This decision was also justified by
the previous significant delay in the diagnosis. Due to the non-diagnostic result of the first biopsy, it was advisable to collect as much material as possible for repeat histopathological examination. During this extended biopsy, approximately 90% of the tumor mass was safely removed. The lesion was not removed in its entirety due to disagreement with such an extensive procedure given the unknown nature of the tumor. The decision for further treatment was made during the oncology consortium.

Diagnosis of SNUC is based on a combination of contrast-enhanced computed tomography and magnetic resonance imaging to assess the local tumor grade, as well as the presence of altered neck lymph nodes. The tumor grade is most often classified according to the American Joint Committee on Cancer (AJCC) system [6]. In case of suspicion of distant metastases positron emission tomography (PET) or computed tomography of the chest is recommended [6]. At the time of diagnosis, our patient was diagnosed with stage IVA disease due to the large tumor size and the absence of distant metastases on PET scan. One and a half years later, when imaging studies described the presence of distant bone metastases, the patient is at disease stage IVC.

On histopathological examination, SNUC is characterized by pleomorphic cells with a high nuclear-cytoplasmic ratio arranged in nests, lamellae, and beads without squamous differentiation, sometimes with increased dysplasia of the overlying epithelium [3, 4]. Tumor cells contain a small amount of eosinophilic cytoplasm with a medium to large nucleus and a delicate cell membrane. High mitotic activity, foci of necrosis and apoptosis are characteristic. Lymphovascular infiltration and neuroinvasion are frequently observed [3, 5]. Immunohistochemical staining is crucial for the diagnosis of SNUC. Most patients with SNUC show expression of epithelial markers: pancytokeratins (AE1/AE3), low molecular weight cytokeratins (CK) and others (CK 7, 8 and 19) and no response to CK 5, 6 and 14, which is important in differentiating SNUC from squamous cell carcinoma.

SNUC shows variable reactivity for P63 protein, epithelial membrane antigen (EMA) and neuron-specific enolase (NSE), while synaptophysin, chromogranin, S100, vimentin and Leu-7 are negative or focal positive [2, 3, 5].

The prognosis in SNUC is unfavorable. It is associated with late diagnosis of the disease, usually at T3–T4 stage, when extensive local infiltration with involvement of the skull base, dura mater or orbit is present [4, 5, 8]. As many as 10–30% of patients present with neck lymph node metastases at the time of diagnosis, while distant metastases appear later [9]. Compared to other neuroendocrine tumors such as olfactory neuroblastoma, SNUC has a higher rate of local recurrence and a greater propensity for distant metastasis via the vascular route and by neuroinvasion [5]. In addition, due to the rarity of the disease, there are no well-defined standards of therapeutic management. The 5-year overall survival according to different data ranges from 6.25 to 74% [5]. In a study by Chambers et al. that analyzed data from 318 patients with SNUC, the 5- and 10-year survival rates were 34.9% and 31.3%, respectively, with a median survival of 22.1 months [10]. In a multicenter study by de Bonnecaze et al. involving 54 patients with SNUC, the 3-year overall survival and recurrence-free survival were 62.4% and 47.8%, respectively [11].

Treatment of SNUC should be an aggressive combination therapy, combining surgical resection, radiotherapy, and chemotherapy. According to the literature, tri-modal treatment provides better local control compared with the dual-modal approach, but no consistent treatment sequence scheme has been established [1, 2, 5].
itself, more easily achieve control of surgical margins and spare critical structures such as the orbit [12]. Moreover, it is believed that the implementation of induction chemotherapy may reduce the incidence of distant metastases. On the other hand, neoadjuvant chemotherapy may be associated with prolonged toxicity of treatment [5]. In the de Bonnecaze study, only neoadjuvant chemotherapy was associated with a significant improvement in relapse-free survival in multivariate analysis [11].

CONCLUSIONS

SNUC is a rare cancer with high aggressiveness. Histopathological examination of the tumor with immunohistochemical staining is most important in diagnosis and differentiation. SNUC is associated with a poor prognosis, with a high rate of local recurrence and distant metastasis, so early diagnosis and differentiation with other malignant tumors of the nasal and sinus cavities, especially neuroendocrine tumors, is extremely important. Treatment is based on combination therapy combining chemotherapy, radiotherapy and surgery.

Currently, one of two regimens is preferred: 1) surgery followed by complementary radiotherapy/radiochemotherapy or 2) definitive radiochemotherapy with or without neoadjuvant chemotherapy. It is difficult to compare the results of these different treatments given the rarity of the tumor and the small number of cases included in most studies [5]. According to many authors, extensive craniofacial resection should always be performed when the tumor is operable with subsequent radiotherapy. This is the treatment that most improves the patient’s prognosis, and surgical reduction of the tumor mass further reduces the radiation dose and its side effects during subsequent radiotherapy [5]. This treatment regimen is often combined with adjuvant or neoadjuvant chemotherapy due to high recurrence rates.

The presence of neck lymph node metastases is a poor prognostic indicator [12]. The recurrence rate when scheduled neck irradiation is omitted is as high as 50–60% compared to 0% in patients, after radiotherapy including the neck [13].

Neoadjuvant chemotherapy is recommended prior to surgery for cytoreductive treatment, in addition, it may facilitate the surgery
REFERENCES


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