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High-Grade Large Cell Neuroendocrine Cancer of Ethmoid Sinus

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Abstract

Large-cell neuroendocrine carcinoma (LCNEC) is a rare high-grade malignancy usually found in the lung and gastrointestinal tract. It is uncommon for LCNEC to occur in the paranasal sinuses. Computerized tomography (CT) or magnetic resonance imaging (MRI) with contrast and biopsy by nasal endoscopy are used to diagnose and stage the tumors. Histological confirmation is made by the presence of large cells with immunohistochemical staining positive for synaptophysin and chromogranin-A. We present the case of a 55-year-old White male with no significant past medical history who presented to his primary care doctor with three months of unresolving headaches. He had a rapid progression of symptoms including loss of taste and smell and eventual hypoesthesia of the right palate, diplopia, and pain. CT with and without contrast demonstrated a 4.9x2.9x2.6 cm mass in the posterior ethmoid sinus invading the cribriform plate and fovea ethmoidalis. Nasal endoscopy with a biopsy of the ethmoid sinus mass revealed that the tumor was a high-grade LCNEC. He underwent craniofacial resection of the tumor for debulking. Repeat CT six weeks after demonstrated regrowth of the mass and invasion of the sphenoid sinus, anterior clinoid process, right inferior and superior orbital fissures, and pterygopalatine fossa with sphenoid roof destruction. He underwent chemotherapy with six cycles of cisplatin and etoposide with complete response and is currently undergoing sequential radiation treatment. This case demonstrates a rare case of LCNEC tumor of the ethmoid sinus, which typically has a poor prognosis. There is limited data on treatment for this rare condition in the literature. Hence, we find it important to document and publish each case to aid clinicians in determining appropriate treatment for patients with similar condition. We have also done a SEER database analysis and literature review of all reported cases of sinonasal LCNEC.

Keywords: Neuroendocrine cancer; large cell; sinonasal carcinoma; head and neck cancer; chemotherapy; radiation; SEER database; ethmoid sinus; SNUC

Background

Cancers of paranasal sinus (PNS) are rare and constitute only around 3% of all the head and neck cancers [1]. Majority of these arise in the maxillary sinus, and a very small proportion constitute ethmoid sinus tumors (EST). It is more common in males. The most common histology is squamous cell carcinoma, adenoid cystic, adenocarcinoma and esthesioneuroblastoma [2]. Rare histology tumors often arise in ethmoid sinus including sarcoma, lymphoma, sinonasal undifferentiated

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carcinoma (SNUC), small cell neuroendocrine cancer (SCNEC), and large cell neuroendocrine carcinomas (LCNEC). The most common presenting symptoms of PNS tumors are facial pain, headache or nasal obstruction [3]. In initial stages, ESTs are often asymptomatic or have minor symptoms of nasal stuffiness. Locally advanced lesions can extend into the anterior cranial fossa through cribriform plate resulting in anosmia and into the orbit through lamina papyracea causing retroorbital pain or diplopia. Diagnosis is established by imaging with computerized tomography (CT) or magnet resonance imaging (MRI) with contrast and biopsy by nasal endoscopy. Origin of malignancy in ethmoid sinus itself confers poor prognosis compared to other PNS tumors [4]. Metastatic cervical lymph node involvement is rare with ESTs compared to other head and neck malignancies and is a poor prognostic feature [5].

LCNEC which is found more often in lung and gastrointestinal tract is rare to arise from PNS. Histological findings include trabecular pattern of growth, peripheral palisading, necrosis, abundant cytoplasm, and coarse or vesicular chromatin. Pathologic diagnosis is typically confirmed by cell morphology along with the presence of immunohistochemical (IHC) markers of neuroendocrine differentiation like synaptophysin and chromogranin A. High grade tumors have worse survival compared to lower grade tumors [6]. Due to the rarity of the condition, there is limited data guiding treatment. Treatment decisions are often made from extrapolated evidence from studies on SCNEC or SNUC and few case reports of LCNEC of ethmoid sinus. We present the case of a patient with locally advanced LCNEC of ethmoid sinus. Although the clinical presentation, management, and outcome of this patient is crucial in understanding this rare malignancy, it is merely to be used as a guide to treat future patients with this malignancy.

Case Presentation

We present the case of a 55-year-old White male with no significant past medical history that had three months of unresolving headache. He was a former smoker with 10 pack-year history and quit 22 years ago. He presented to his primary care provider and was started on treatment with oral antibiotics for suspicion of sinusitis. Symptoms did not improve with treatment. The headache was worse on lying down and was associated with loss of taste and smell. He later developed numbness at the roof of his mouth on the right side. A computerized tomography (CT) with and without contrast demonstrated a 4.9x 2.9x 2.6 cm mass in the posterior ethmoid sinus invading the cribriform plate and fovea ethmoidalis (Figure 1).

CT of the neck, chest, abdomen and pelvis did not show any other site of disease. MRI brain and orbit confirmed the

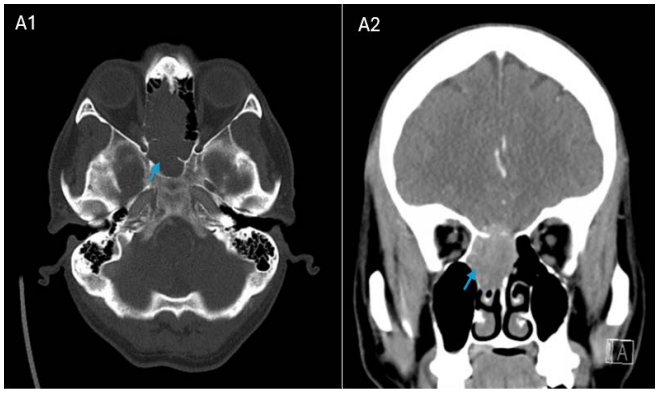

Figure 1: Axial (A1) and Sagittal (A2) views of CT of head and face with contrast at diagnosis (A1, A2) with contrast showed 2.9x 2.6x 5 cm mass = involving the right superior nasal passage, ethmoid air cells, and sphenoid sinus with local osseous destruction and septal resorption (marked by yellow arrow). It penetrates the cribriform plate with an intracranial component lying along the distribution of the right olfactory glove. No intra-axial infiltration of the right frontal lobe was noted.

findings. Patient's symptoms worsened rapidly and developed diplopia and pain behind right eye in the next two weeks. He underwent nasal endoscopy with biopsy of the ethmoid sinus mass. Pathology revealed high grade LCNEC with Ki-67 of 95% and mitotic count of 30-40/10 high power field (HPF). Due to rapid worsening of symptoms, he underwent craniofacial resection of the PNST for debulking with nasoseptal flap and repair of dura mater. The tumor was found to have invaded skull base during the surgical procedure. The surgery was complicated by cerebrospinal fluid leak requiring transsphenoidal repair. A repeat CT scan six weeks following surgery showed persistent large central skull base mass now involving sphenoid sinus, anterior clinoid process, right inferior and superior orbital fissures, and pterygopalatine fossa with sphenoid roof destruction.

Since the tumor was located near the optic chiasm and right optic nerve, treatment with radiation was concerning

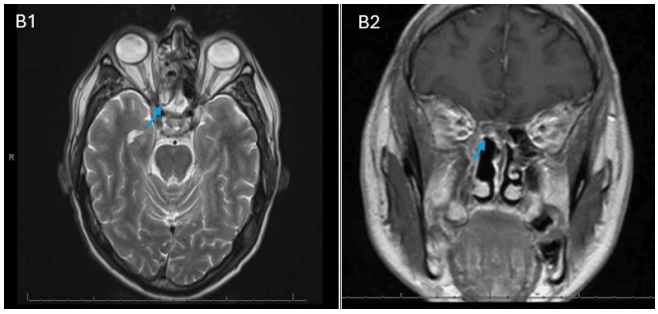

Figure 2: Axial (B1) and sagittal (B2) views of MRI brain post-chemotherapy with previous frontal craniotomy changes, with rim enhancing signal abnormality involving the frontal sinuses and extending to the superior margin of the ethmoid air cells measuring 2.3x4.4cms.

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Table 1: SEER database of patients with sinonasal LCNEC diagnosed between 2000-2018.

Age group	Sex	Year of diagnosis	Race	Grade	Laterality	Primary	TNM (Stage)	Surgery	Alive/Dead (Cause)	Survival (months)
55-59	M	2005	White	UD/A	NA	ES	T4aN0M0 (IVA)	Yes	Dead (Cancer)	29
65-69	F	2005	White	UD/A	Right	MS	T4bN0M0 (IVB)	NR	Dead (Other)	0
55-59	F	2005	White	Grade 3	NA	ES	T4bN0M0 (IVB)	NR	Alive	162
55-59	M	2006	White	UD/A	NA	ES	Unstaged	Yes	Dead (Cancer)	8
65-69	F	2012	White	Grade 3	NA	ES	T4N0M0 (IVB)	NR	Alive	74
55-59	M	2014	Asian/Pacific Islander	UD/A	Right	MS	T4aN2bM0 (IVA)	NR	Dead (Cancer)	1
60-64	F	2014	White	Grade 3	NA	Other	T1N0M0	Yes	Alive	51
35-39	M	2017	White	NA	NA	ES	N0M0 (Locally adv)	Yes	Alive	13
85+	F	2017	White	UD/A	Right	MS	N0M0 (Locally adv)	NR	Dead (Other)	3
70-74	M	2018	White	NA	NA	Other	N0M1 (bone mets)	Yes	Alive	6
70-74	M	2018	White	NA	Right	ES	N0M0	NR	Alive	4

M: Male, F: Female, UD/A: undifferentiated/anaplastic, NR: Not Recommended, NA: not available, ES-ethmoid sinus, MS-maxillary sinus

due to the potential side effects of visual defects. Hence, he was started on chemotherapy with cisplatin 60mg/m2 Day 1 and etoposide 100mg/m^2 Days 1-3 repeated every 21 days with plans to add radiation after adequate cytoreduction. Chemotherapy resulted in clinical response with symptomatic improvement within 2 weeks of initiation of treatment. He had complete resolution of symptoms after 2 cycles of chemotherapy and discontinued all pain medications. MRI after 4 cycles showed significant reduction in tumor size with enhancing signal now involving only the frontal sinuses, extending to the superior margin of the ethmoid air cells measuring 2.3x4.4cm (Figure 2). After completing 6 cycles of chemotherapy, he is currently undergoing radiation with a target dose of 70 Gy.

Discussion

NECs of the sinonasal tract are extremely rare, often poorly differentiated with high malignant potential and have an overall poor prognosis. These tumors are again subdivided into small-cell and large-cell NECs. Retrospective registry analysis of sinonasal NECs, especially the LCNEC category is difficult due to lack of proper classification. These tumors are often classified under SNUC or Not Otherwise Specified (NOS) leading to underrepresentation of this entity in clinical studies.

SEER database analysis: With the above limitations in mind, we reviewed all cases of sinonasal LCNEC in SEER database between 2000-2018 and identified 11 patients (Table 1). 90.9% of the patients were over 55 years of age. All but one patient was White. Ethmoid sinus was the predominant site of origin (54.5%), followed by maxillary sinus (27.2%). 7 out of the 11 patients presented in locally advanced/metastatic stage. Five patients underwent surgery while it was not reported in the remaining patients and the database lacked information on RT or chemotherapy. The median survival of this patient group was 8 months with only 6 patients remaining alive at follow-up.

Literature review: Our review of existing literature for reports of sinonasal LCNEC yielded 18 cases (Table 2). Majority of the patients were male (70.6%). Median age was 66 (range 14-82 years). Nasal obstruction was the most common presenting symptom (66.7%) followed by ocular symptoms (55.5%). 82% cases with staging information available were stage IVA/B (per AJCC 8th edition staging) with only one case being metastatic at diagnosis. Cytokeratin and synaptophysin were universally positive in all cases which reported these IHC stains while chromogranin-A was positive in all except two cases. Median Ki-67 index was 60% (range 30 to >80%) and mitotic index 20/HPF (range 6-33/HPF). Most of the patients underwent multimodality treatment with surgery (68.8%), radiation (100%) and chemotherapy (81.3%) involved in varying sequence. Seven patients had complete response while 5 died from the malignancy. Survival ranged between one month to 53 months. In a study of 10 LCNECs of head and neck (including three cases of sinonasal primary included in the review), HPV positivity was found in 3 cases including one in the sinonasal tract. However, HPV-positivity did not impart a prognostic advantage in this group [7].

Treatment decisions for sinonasal LCNEC is mostly extrapolated from studies on patients with SNUC. Based on

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Table 2: Cases of sinonasal LCNEC from review of literature with clinicopathological characteristics.

Age, Sex	Presenting symptoms	Imaging finding	TNM stage	IHC	Treatment	Outcome	Ref
70M	Epistaxis, nasal obstruction	Right NC mass with invasion of nasolacrimal duct.	stage II cT2N0M0	CK, CgA, Syn, CD56 +. Ki67 80%, MI 10/HPF.	Endoscopic resection, ethmoidectomy, maxillary antrostomy. Adjuvant cisplatin+ etoposide x6 cycles and sequential EBRT	CR at 6m	[14]
68F	Right eye swelling, pain and proptosis	Right orbital mass extending to all PNS, orbital wall and skull base.	stage IVA cT4bN0M0	CgA, CD56, EMA+. MI >10/ HPF	Unresectable. Cisplatin + etoposide and RT (sequence unknown)	NED at 36m	[15]
40M	Nasal obstruction, anosmia x1m	Tumor involving all PNS and left NC, eroding adjacent bones and involving bilateral frontal lobes.	Stage IVB cT4bN0M0	CK, CgA, Syn, CD56, Ki67 +	Neoadjuvant nedaplatin, etoposide x 1cycle with incomplete response. Then concurrent chemoRT x2 cycles followed by chemo alone x3 cycles. (EBRT 6996 cGy with 212 cGy/fr to carcinoma, 5040 cGy with 180 cGy/fr to PNS, nasal cavity, upper neck). No surgery.	CR at 10m	[16]
81M	Asymptomatic at diagnosis. Headache, eye pain, ptosis after 2 weeks.	Right ES mass involving right NC, maxilla, orbit, cribriform plate, intracranial fossa and bone destruction.	Stage IVB cT4bN0M0	CK, CgA, Syn +	Concurrent chemoradiation with cisplatin-etoposide, 7 cycles.	PR after treatment	[17]
68M	NA	Large sinonasal mass, neck metastasis	NA	CK, Syn, CD56 +	Chemotherapy and RT (sequence unknown)	DM, DOD at 18m	[7]
70F	NA	Sinonasal mass with intracranial extension and bone erosion	NA	CK, Syn, CD56, p63 +	Surgical resection, chemotherapy and RT (sequence unknown)	AWD at 9m	[7]
58M	NA	Sinonasal mass with intracranial extension and bone erosion	NA	CK, CgA, Syn, CK5/6, p16, HPV-ISH +	Surgical resection, chemotherapy and RT (sequence unknown)	DOD at 12m	[7]
14F	NA	NC mass	NA	CK, CgA, Syn, p16 +	Not treatment plan at the time of publication	AWD at 1m	[7]
73M	Right nasal obstruction and epistaxis for 2yrs	Right NC mass with involvement of right FS, bilateral ES and MS	Stage IVA cT4aN0M0	CK, CgA, Syn, CD56+. CK5/6, CK7 equivocal	Right lateral rhinotomy, medial maxillectomy. Adjuvant RT (55Gy in 20fr over 1 month)	NED at 20m	[18]
56F	Exophthalmos, chemosis, headache, nausea, anosmia	Left nasal cavity mass expanding into all paranasal sinuses, the left frontal lobe, left orbit	Stage IVB cT4bN0M0	NA	Endonasal, transcranial debulking. Adjuvant chemoRT- 4 cycles of cisplatin 80mg/m^2/d for 1 day and etoposide 100mg/m^2/d D1-3. Concurrent 40Gy/20fr and boost stereotactic RT to tumor origin	NED at 18m	[19]
39M	NA	NC mass	cT4N0	Ki67 39%, MI 33/ HPF.	Surgery and RT	NED 45m	[20]
42M	NA	ES mass	cT3N0	Ki67 80%, MI 33/ HPF	Surgery, chemotherapy and RT	DOD at 26m	[20]
80M	NA	NC mass	cT3N2	Ki67 30%, MI 6/ HPF	Surgery, concurrent chemoRT	DOD 53m	[20]
66M	NA	NA	Stage IVA cT4aN0M0		Endoscopic resection, concurrent chemoRT and sequential RT	DOC 21m	[21]

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82M	Right nasal congestion, epistaxis for 4yrs	Right ES mass eroding medial bony wall of orbit, cribriform plate, SS and FS	Stage IVA cT4aN0M0	CgA, Syn, CD56, EMA +	Surgery recommended; patient refused. Radical RT.	NED at 30m	[22]
60M	Right nasal obstruction and lacrimation	Right MS expansile mass eroding lateral nasal wall, and inferior orbital wall	Stage IVA cT4aN0M0	CK, Syn, CD56, INSM1+. Ki67 >80%, MI >20/ HPF.	Total maxillectomy. Neoadjuvant chemoRT with cisplatin + etoposide and RT 70Gy	LR in 2m	[23]
45F	Right nasal obstruction x 1 year, epiphora right eye	Exophytic 3x4cm right NC mass. C4 vertebral mets, 3.1cm neck lymphadenopathy	Stage IVC	CK, Syn+, Negative for NSE, CgA, CD56, p40, CK 5/6. Ki67 60%.	Endoscopic resection. Concurrent Cisplatin, etoposide, docetaxel q3w x2 cycles (intolerance) IMRT 50Gy/22fx in 37d to primary and 10Gy/5fx to mets	DOD at 6m	[24]
NA	NA	4.1 cm bilateral ES mass extending to NC, MS, FS, left orbit and anterior cranial fossa with erosion of bone.	Stage IVB cT4bN0M0	CK, Syn, EMA, S-100 +. Negative for CgA, CK5/6, Vim. Ki-67 60%,	NA	NA	[25]

Abbrev.: NC- nasal cavity, ES-ethmoid sinus, SS-sphenoid sinus, MS-maxillary sinus, FS-frontal sinus, CK-cytokeratin, CgA- chromogranin A, Syn-synaptophysin, EMA-epithelial membrane antigen, Vim-vimentin, MI-mitotic index, RT-radiotherapy, IMRT-intensity mediated RT, EBRT- external beam RT, NED- no evidence of disease, CR- complete response, PR- partial response, LR- local recurrence, DM- distant metastasis, AWD- alive with disease, DOD- dead of disease, DOC- dead of other causes.

the limited evidence and poor outcomes with single modality treatments, recommendations from National Comprehensive Cancer Network (NCCN) are to include systemic therapy routinely to the overall treatment of patients with SNUC with neuroendocrine features. Combined modality treatment including surgery, chemotherapy and/or radiation have shown to be the major factor affecting local and regional control, however with increased toxicity [8, 9]. Although surgical resection is often considered similar to squamous cell or adenocarcinoma of sinonasal tract, it is limited in NEC due to the involvement of critical structures such as brain, cranial nerves, and eyes and incomplete resection is common. However, with improved surgical techniques and reconstruction, the complications and morbidity from the procedures have been reduced in recent times [10]. Incomplete resection, high risk pathologic features like high-grade disease, positive margins, intracranial and/or intraorbital extension necessitates need for systemic chemotherapy and radiation among these patients. Radiation alone or concurrent chemoradiation is commonly employed as neoadjuvant or adjuvant treatment. RT for paranasal sinus tumors can be associated with risk of blindness, which is reduced with intensity modulated radiation techniques [11].

In a retrospective study of 95 patients with SNUC, concurrent chemoradiation (platinum-etoposide with 60-70 Gy at 2Gy/fraction) after induction chemotherapy (cisplatin 60-80mg/m2 on D1 and etoposide 100-120mg/m2 or docetaxel 75mg/m2 on D1-3 every 21 days) and resection was associated with a 5-year disease-specific survival rate of 81% (95% CI 69-88%), compared to 59% (95% CI 53-66%) in the entire study population [12]. After partial response to induction chemotherapy, surgery and adjuvant chemoradiation, the disease-specific survival was however lower at 39% (95% CI 30-46%). The patients who did not have at least partial response to induction chemotherapy had 5-year disease-specific survival (DSS) of 0% (95% CI 0-14%). In an analysis of SNUC cases from National Cancer Database between 2003-2014, surgery followed by chemoradiotherapy was associated with improved survival than definitive chemoradiotherapy alone (55.8% vs 42.6%, $p = 0.007$) [13]. However, these results may be skewed with patients with late-stage disease not receiving surgery. In late-stage tumors, there was no difference in survival between both groups ($p = 0.22$). The positive margin was associated with poor survival with 5-year survival of 0%. It should also be noted that awaiting surgical wound healing and possible surgical complications may delay the initiation of chemotherapy and radiation. Hence in our opinion, upfront surgical resection should be reserved for early-stage disease and advanced-stage symptomatic disease from tumor mass. For metastatic disease which carries a very poor prognosis, systemic chemotherapy with platinum and etoposide with or without concurrent RT as used in high-grade neuroendocrine tumors is recommended. The use of immunotherapy remains unclear and is recommended based on tumor agnostic indications like high tumor mutation burden or microsatellite instability-high tumors.

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