

# Large-cell neuroendocrine carcinoma of nasal cavity and paranasal sinuses after successful curative therapy: a case report and literature review

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**Abstract:** This report describes a 40-year-old male patient with symptoms affecting the nasal sinuses including nasal obstruction and olfactory anesthesia. Magnetic resonance imaging demonstrated that the tumor eroded the adjacent bone and bilateral frontal lobes. The biopsy sample of the left nasal mass was processed for both H&E staining and immunohistological staining for various markers. The final histological examination showed large-cell neuroendocrine carcinoma with poor differentiation. After a general evaluation, the patient was staged as cT4bN0M0. The patient was treated by combined radiotherapy and chemotherapy. The treatment yielded almost complete remission, and after 10 months of follow-up, no distant organ metastasis or recurrence in the primary tumor region was detected. We report this rare case and review the current literature of this tumor.

**Keywords:** nasal cavity and paranasal sinuses carcinoma, large-cell neuroendocrine carcinoma, pathology, radiotherapy

## Introduction

Large-cell neuroendocrine carcinoma (LCNEC) is a rare epithelial neuroendocrine malignancy and is preferentially located in the gastrointestinal tract and pancreas.<sup>1</sup> Cases of LCNEC have been reported in many other locations, including the thymus, gallbladder, prostate, larynx, salivary glands, nose, nasopharynx, tonsil, hard palate and mastoid.<sup>2–5</sup> However, LCNEC of the nasal cavity and paranasal sinuses is rarely reported.

Classification of nasal cavity and paranasal sinus carcinomas is manifold. The WHO published the extensively revised 4th edition of the Classification of Head and Neck Tumors in 2017. Although LCNEC was not previously acknowledged, the new edition recognizes small-cell neuroendocrine carcinoma and LCNECs as distinct types.<sup>6</sup> Radiotherapy as a treatment option for nasal cavity and paranasal sinus carcinomas has been widely investigated, but no studies have reported its effects on LCNEC. We present the case of a male patient with LCNEC located in the nasal cavity and paranasal sinuses who underwent successful radiotherapy and chemotherapy and achieved a clinically complete recovery.

## Case report

A 40-year-old male patient was initially diagnosed with nasal polyps at a local county hospital after he presented with symptoms of nasal obstruction and olfactory anesthesia. However, the symptoms significantly worsened within 1 month. The

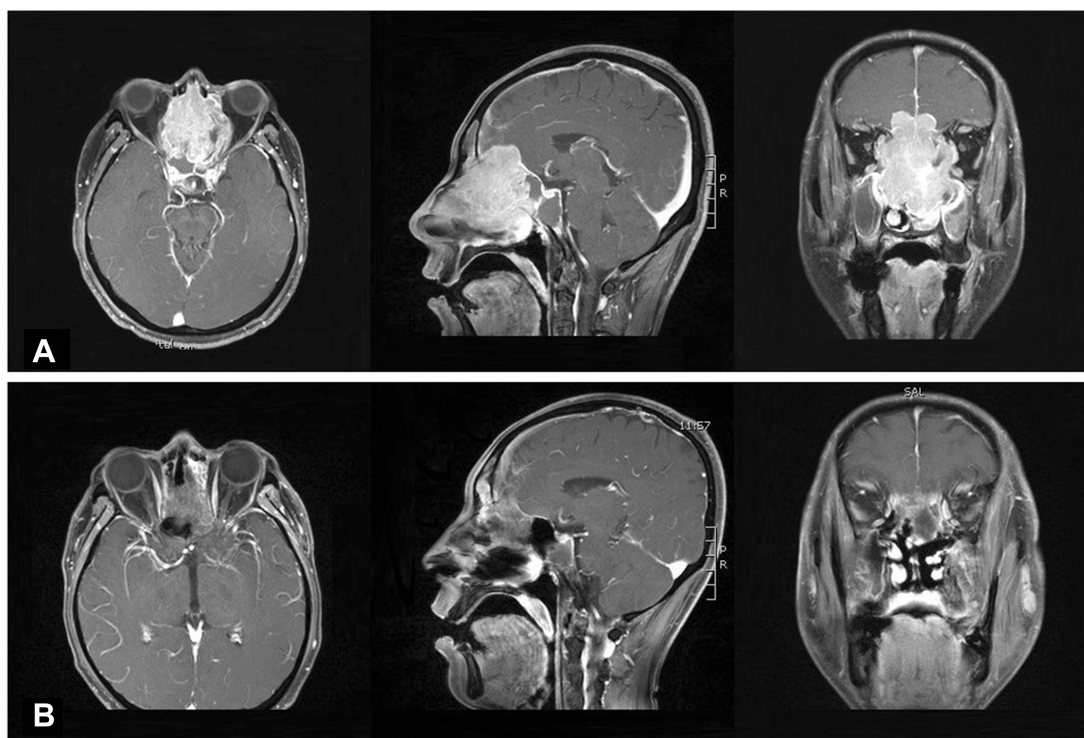
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patient was thereafter admitted to the First Hospital of Jilin University. Contrast-enhanced magnetic resonance imaging (MRI) demonstrated that a tumor was located in the bilateral maxillary sinus, ethmoid sinus, frontal sinus, sphenoid sinus and left nasal cavity without enlarged lymph nodes in the bilateral neck. The maximum diameter of the tumor was 7.0×5.2 cm, and the tumor eroded the adjacent bones including the bilateral maxillary sinus medial wall, sieve plate, sphenoid sinus, frontal sinus wall and bilateral frontal lobes (Figure 1A). A biopsy of the patient's left nasal mass was performed. To characterize the cells, the biopsy sample was processed for both conventional H&E staining and immunohistological staining for various markers. The LCNEC was positive for Ki-67, CKpan, CgA, Syn and CD56. Additional stains for HMB45, S-100, Vimentin, EBER, CD20 and CD3 were negative. The final histological examination showed LCNEC with poor differentiation (Figure 2).

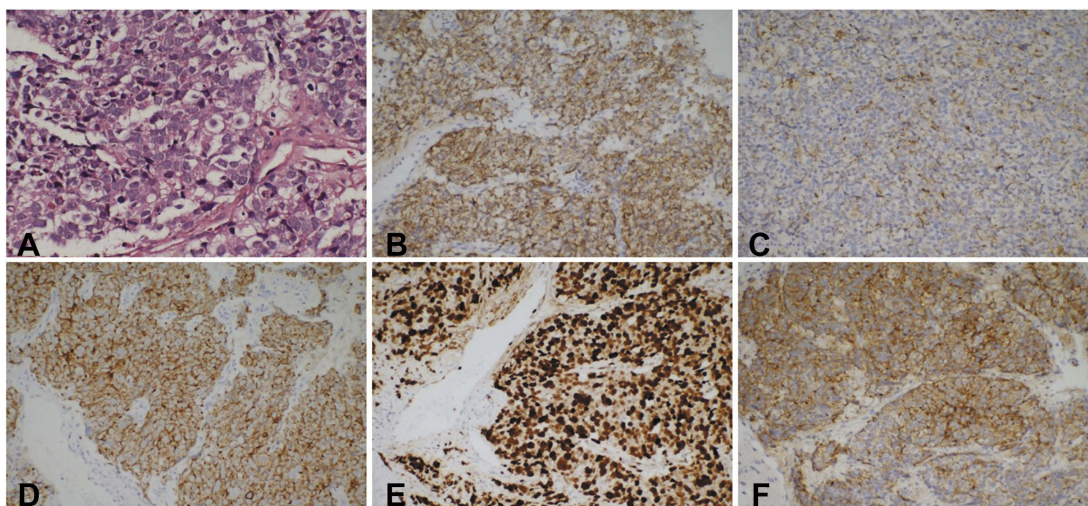
This patient did not undergo positron emission tomography/computed tomography (PET-CT) scan due to economic reasons. After a general evaluation, the patient was staged as cT4bN0M0 according to the staging system established by American Joint Committee on Cancer (AJCC) in 2010. The

patient received one cycle of neoadjuvant chemotherapy (etoposide combined with nedaplatin, EP regimen); however, the symptoms did not improve significantly. So we decided to give concurrent radiochemotherapy after multidisciplinary consultation. External radiation therapy (RT) was administered with the TrueBeam linear accelerator using volumetric modulated arc therapy (VMAT). A total dose of 5,040 cGy with 180 cGy/fraction was applied to the bilateral maxillary sinus, ethmoid sinus, frontal sinus, nasal cavity, and upper neck region (levels II-III), while a total of 6,996 cGy with 212 cGy/fraction was applied to the carcinoma of the nasal cavity and paranasal sinuses. During RT, the EP regimen was administered in 2 cycles. Following concurrent radiochemotherapy, the patient was treated with three cycles of sequential adjuvant chemotherapy (EP regimen).

After chemoradiotherapy, the treatment led to almost complete remission (CR) as assessed with the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Figure 1B), and no adverse reactions were reported. After 10 months of follow-up, no distant organ metastasis or recurrence in the primary tumor region was detected. The short-term treatment is an effective therapy, although the follow-up is only 10 months, and long-term follow-up work still needs to be continued.



**Figure 1** MRI of the nasal cavity and paranasal sinuses. **(A)** Contrast-enhanced MRI shows a huge tumor located in the nasal cavity and paranasal sinuses eroded not only the adjacent bone but also bilateral frontal lobes. **(B)** Contrast-enhanced MRI shows the tumor was almost completely disappeared 1 month after radiotherapy and chemotherapy. **Abbreviation:** MRI, magnetic resonance imaging.



**Figure 2** Histopathology of LCNEC. (A) H&E staining: tumor cells in the subepithelial stroma showed nest infiltration. The cells are large in volume, rich in cytoplasm and vacuolated or eosinophilic and have a large nucleoplasmic ratio. The nucleus is round or elliptical, the chromatin is deeply stained, and the granules are coarse and granular, and the obvious eosinophilic nucleoli can be seen (400×magnification). Immunohistological staining showing tumor positivity for CD56 (B), CgA (C), CKpan (D), Ki-67 (E) and Syn (F). **Abbreviation:** LCNEC, large-cell neuroendocrine carcinoma.

## Discussion

Sinonasal carcinomas are a rare group of malignant neoplasms that arise in the nasal cavity or its adjacent paranasal sinuses. Sinonasal carcinomas comprise 5% of head and neck cancers and fewer than 1% of all malignant tumors.<sup>7</sup> The overall annual incidence of sinonasal carcinoma is 0.556 cases per 100,000 people with a male/female ratio of 1.8:1. The most common histologies are squamous cell carcinoma (51.6%) and adenocarcinoma (12.6%), whereas the most common primary sites are the nasal cavity (43.9%) and maxillary sinus (35.9%).<sup>8</sup> The prognosis of patients with sinonasal cancer is generally poor and has not changed substantially over the last 3 decades.<sup>8</sup> Due to the development of multidisciplinary therapy, the 5-year survival rate of sinonasal carcinomas was significantly higher in 2010–2014 (65%) than in 1980–1984 (46%).<sup>9</sup>

Sinonasal neuroendocrine carcinoma (SNEC) is a rare and high-grade malignant epithelial neoplasm that is usually associated with a poor prognosis as well as immunohistochemical features of neuroendocrine differentiation. Tapan et al<sup>7</sup> analyzed the clinical pathological characteristics and survival outcomes of SNEC and found that the overall 5-year disease-specific survival (DSS) rate for SNEC was 50.8%. Five-year survival analysis for SNEC by site revealed DSS rates of 80.7%, 59.2%, 34.5% and 33.0% for the sphenoid sinus, nasal cavity, maxillary sinus and ethmoid sinus, respectively.

SNEC is separated into small-cell and large-cell types. LCNEC is much rarer and presents unique challenges both

in diagnosis and in treatment. The clinical presentations of sinonasal LCNEC include nasal obstruction, epistaxis, nasal drainage, facial mass and facial pain, and there is no clinical difference between both small-cell and large-cell type. However, the large-cell subtype shows a better survival rate than that of the small cell.<sup>10</sup> These symptoms overlap with other those of benign sinonasal diseases and often delay diagnosis and appropriate treatment. This patient was diagnosed with a locally advanced tumor that developed rapidly; however, it was not accompanied by the enlarged lymph nodes in the bilateral neck that are typical of this disease. LCNEC is a high-grade neuroendocrine neoplasm and generally associated with poor prognosis. However, tumor staging appears of limited value in predicting survival or selecting a treatment strategy.<sup>11</sup> Although the patient was diagnosed with an advanced and rapidly developing tumor, chemoradiotherapy was an effective and successful treatment.

Histologically, LCNEC is characterized by 1) large, polygonal cells with coarse nuclear chromatin and prominent nucleoli, 2) high mitotic rate and frequent necrosis, 3) architectural patterns suggestive of neuroendocrine differentiation (organoid nests, trabeculae, rosettes and/or peripheral palisading) and 4) immunohistochemical evidence of neuroendocrine differentiation (ie, immunostaining with Syn, CKpan, CgA and/or CD56).<sup>12</sup> Because there is not yet an immunohistochemical stain that can discriminate between small-cell neuroendocrine carcinoma (SCNEC) and LCNEC, a panel of three



markers, BAI3, CDX2 and VIL1, was used for diagnosis.<sup>13</sup> The critical distinction between SCNEC and LCNEC is not in the overall cell size but in the nuclear to cytoplasmic ratios (“high” in small cell and “lower” in large cell).<sup>14</sup> The major feature that distinguishes LCNEC from atypical carcinoids is mitotic activity ( $>10/10$  high-power fields or  $2\text{ mm}^2$ ) and necrosis, with LCNEC typically having more extensive necrosis and more pleomorphic cells with prominent nucleoli.<sup>15</sup>

CT and MRI are the most commonly used techniques to determine the location and local extension of SNEC. CT has several advantages in evaluating skeletal changes such as cortical erosion, destruction and thickening of bones. However, MRI is complementary to CT because it can effectively characterize soft tissue components and evaluate the extent of tumor invasion beyond the bony sinus walls.<sup>16</sup> The utility of [ $^{18}\text{F}$ ]fluorodeoxyglucose (FDG)-PET/CT imaging is not recommended for routine diagnosis and staging of head and neck cancer in most guidelines;<sup>17</sup> however, it has been shown to be useful for the imaging of residual and recurrent tumors.<sup>18</sup>

Van der Laan et al<sup>11</sup> found that the most important predictors of survival in SNEC are differentiation grade and the associated choice of treatment modality. Furthermore, they recommended that surgery should be the cornerstone of treatment, supplemented by radiotherapy in poorly differentiated subtypes. The optimal treatment of LCNEC is a complicated issue due to the low numbers of patients and the staggering amount of different histologies. Prospective studies are scarce; a search of the PubMed database revealed only a few case reports and small retrospective case series. The treatment of LCNEC is controversial and not yet standardized because there are no clinical trials that define the optimal treatment approach for either localized or advanced disease. Some suggest a multimodal approach to the treatment of sinonasal carcinomas which includes surgical resection, chemotherapy and radiotherapy.

Surgery is the preferred treatment in the majority of sinonasal carcinomas. Resection of tumors with clear margins leads to an excellent prognosis. However, this patient was diagnosed in an advanced state, and complete surgical resection would be difficult. Hanna et al<sup>19</sup> retrospectively analyzed 120 patients who underwent endoscopic resection of sinonasal cancer between 1992 and 2007, and approximately 10% of the tumors had an intracranial epicenter, most commonly around the olfactory groove. Tumors extended to or invaded the skull base in 20% and 11% of the patients, respectively.

The oncologic outcomes of patients with sinonasal carcinomas have been improved, likely due to more effective

reconstruction using vascularized flaps and more effective adjuvant therapy, particularly intensity-modulated radiation therapy (IMRT). Radiotherapy may provide effective local control for patients with moderately differentiated NEC if resection is not feasible, while post-RT surgical resection can benefit patients with chemoresistant or radioresistant disease.<sup>20</sup> Postoperative RT was usually used in patients with high-grade tumors, advanced T stage, bone invasion, perineural spread, intracranial extension, dural or brain involvement or positive margins. Duprez et al<sup>21</sup> retrospectively analyzed 130 patients with nonmetastatic sinonasal tumors who were treated with IMRT. In this study, we did not observe Grade 4 acute ocular toxicity, and neither radiation-induced blindness nor severe dry eye syndrome was observed in late toxicity. IMRT for sinonasal tumors should be considered as the standard radiotherapy for patients who are not surgically treated.

The patient received VMAT, a new RT treatment delivered using a continuous arc motion of the gantry with simultaneous variation of the multileaf collimator position, gantry speed and dose rate, with the ability to produce highly conformal plans in a short time.<sup>22</sup> VMAT achieved a better conformity and more homogenous target coverage compared with IMRT. Additionally, VMAT has a faster delivery time and a lower number of monitor units. VMAT can also optimize the radiation dose to the tumor and reduce toxic effects to normal structures, particularly the lens.

There may be also a couple of limitations of the case report. The follow-up time of this case is very short. But LCNEC located in the nasal cavity and paranasal sinuses is rare, and we cannot find sufficient data for survival, local, regional or distant recurrences. A paper showed that the patients with LCNEC of prostate died of their disease within a short period of time after the detection of LCNEC.<sup>5</sup> Another research reported that LCNEC represented an aggressive tumor type and has a poor prognosis, similar to that of small-cell carcinoma.<sup>2</sup> Another limitation is that this patient did not receive the PET-CT scan before chemotherapy and radiotherapy due to economic reasons. We have done other examinations including history and physical, chest and abdominal CT, bone scan and local MRI, and results showed no obvious symptoms of distant metastasis. Based on those examinations, the patient was staged as cT4bN0M0.

## Conclusion

LCNEC is a rare epithelial neuroendocrine malignancy generally associated with poor prognosis. However, staging appears of limited value in predicting survival. Due to the

rarity of LCNEC, a general consensus on the standard therapy has not yet been established. Surgery is the preferred treatment, but radiochemotherapy is also safe and effective.

## Consent to publish

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. This report was approved by the Ethics Committee of The First Hospital of Jilin University.

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## Disclosure

The authors report no conflicts of interest in this work.

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