

Lymphoepithelial carcinoma of the maxillary sinus

A case report and review of the literature

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Abstract

Rationale: Most cases of lymphoepithelial carcinoma (LEC) occur in the nasopharynx, and LEC in the sinonasal tract is extremely rare; thus, the clinical characteristics of sinonasal LEC are not well known.

Patient concerns: A 63-year-old Japanese man presented with a three-week history of left cheek pain, nasal obstruction and cheek swelling.

Diagnoses: Enhanced CT and MRI revealed a tumor of the left maxillary sinus that invaded the left orbit and hard palate, with multiple swollen left cervical lymph nodes. Open biopsy was performed, and the specimen was diagnosed as LEC.

Interventions: Alternating chemoradiotherapy (ALCRT) followed by salvage surgery was performed.

Outcomes: Our patient has been disease free for 5 years.

Lessons: A literature review of the epidemiology, etiology, clinical course and management of sinonasal LEC is highlighted. We believe ALCRT followed by salvage surgery to be a highly optimal treatment for sinonasal LEC from the viewpoint of a balance between quality of life and a high curative effect.

Abbreviations: 5-FU = 5-fluorouracil, ALCRT = alternating chemoradiotherapy, CDDP = cisplatin, CT = computed tomography, EBV = EBV-encoded RNA, EBV = Epstein–Barr virus, FDG = 2-[fluorine-18] fluoro-2-deoxy-D-glucose, MRI = magnetic resonance imaging, NDP = nedaplatin, NPC = nasopharyngeal carcinoma, PET = positron emission tomography, RT = radiotherapy, SUV = standardized uptake value.

Keywords: alternating chemoradiotherapy, Epstein–Barr virus (EBV), lymphoepithelial carcinoma, maxillary sinus, sinonasal tract

1. Introduction

Lymphoepithelial carcinoma (LEC) consists of poorly differentiated squamous cell carcinoma or histologically undifferentiated carcinoma accompanied by prominent reactive lymphoplasmacytic infiltration^[1]. Most cases of LEC occur in the nasopharynx and are pathologically classified as a nonkeratinizing undifferentiated type of nasopharyngeal carcinoma (NPC).^[1,2] Although LEC is generally rare, when present, it tends to be located in various sites in the head and neck,^[3] including the salivary glands, oral cavity, oropharynx, larynx, hypopharynx, lungs, and esophagus.^[4–11] LEC involving the sinonasal tract is rare,

especially in the maxillary sinus.^[1,2] Sinonasal LEC is more common in Southeast Asia, where the incidence of NPC is higher than that in Western countries.^[1,12] Sinonasal LEC is extremely rare in other countries, including Japan, and its clinical characteristics remain unknown.

We herein report a case of LEC of the left maxillary sinus with cervical lymph node metastasis in which 5-year disease-free survival was achieved, and we review the literature on sinonasal LEC.

2. Case report

A 63-year-old Japanese man with a previous history of heavy smoking (20 cigarettes/d × 40 years) and alcohol consumption presented to our hospital in December 2010 with a 3-week history of left cheek pain, nasal obstruction, and cheek swelling. He had no accompanying history of epistaxis, headache, or visual disturbance. His medical history included atrial fibrillation, diabetes mellitus, hypertension and ureteral stone, and his surgical history included operations for appendicitis and sinusitis. An inspection of the nasal cavity with a soft fiberoptic revealed inward displacement of the left inferior turbinate and blockage of the left common nasal meatus (Fig. 1A). A physical examination indicated swelling of his left cheek, left upper gingiva, and left hard palate (Fig. 1B). Enhanced computed tomography (CT) and magnetic resonance imaging (MRI) revealed a 38 × 48 × 50-mm tumor located in the left maxillary sinus that was heterogeneously enhanced with bony destruction of the superior, posterior, and lateral walls, and parts of the anterior wall of the left maxillary sinus (Figs. 2

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Figure 1. Endoscopic findings of the left nasal cavity (A) and oral cavity (B). Inward displacement of the left inferior turbinate and blockage of the left common nasal meatus were found (A). Swelling of the left cheek, left upper gingiva and left hard palate were also observed (B).

and 3). Multiple swollen left cervical lymph nodes were also found on enhanced CT and MRI (Figs. 2 and 3). Positron emission tomography (PET) with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) was performed, and the strong uptake of FDG was observed in the left maxillary sinus (standardized uptake value [SUV]=37.6), lymph nodes of the left parapharyngeal space (SUV=16.6), left tonsil (SUV=25.6), left submandibular lymph nodes (SUV=17.4), and left supraclavicular lymph nodes (SUV=10.2) (Fig. 4).

Approximately 3 weeks after the patient's first presentation to our department, open biopsy with resection from the left upper gingiva was performed, and a specimen was sent for histopathological evaluation. Histology revealed loosely cohesive tumor cells arranged in sheets to trabeculae intermingled with variable numbers of small lymphocytes (Fig. 5A, B). The tumor cells had large round to oval vesicular nuclei, prominent nucleoli, and ill-defined cell borders (Fig. 5A, B). No keratinized cells or intercellular bridges were detected. Immunohistochemical study revealed the tumor cells to be positive for pan cytokeratin, which provided the epithelial nature of the tumor cells, and cytokeratin 14 (Fig. 5C). In situ hybridization to identify small Epstein-Barr virus (EBV)-encoded RNA (EBER) yielded positive results (Fig. 5D), and a pathological diagnosis of LEC was made.

Additionally, EBV serology revealed serum IgG antibodies against the EBV capsid antigen (EBV VCA IgG), serum IgA antibodies against the EBV capsid antigen (EBV VCA IgA), and EBV early antigen (EBV EA IgA) at titers of 1:1280, 1:20, and 1:40, respectively. Based on the clinical, radiological, and pathological findings, a final diagnosis of LEC of the left maxillary sinus with left cervical lymph node metastases (T3N2bM0, stage IVA) was made. His glomerular filtration rate was 55.3 mL/min, suggesting that he had poor renal function due to diabetes mellitus.

Alternating chemoradiotherapy (ALCRT) was performed to treat the LEC of the maxillary sinus based on the regimen for NPC because LEC is common in patients with NPC and because we thought that it might also be effective for LEC of the maxillary sinus. Figure 6 shows a schematic illustration that summarizes the treatment protocol. Although 3 courses of chemotherapy with 5-fluorouracil (5-FU) and cisplatin (CDDP) and 2 courses of radiotherapy (RT) were performed alternately in the original ALCRT regimen, nedaplatin (NDP) instead of CDDP was used to avoid renal dysfunction due to CDDP. In our chemotherapy regimen, 5-FU at a dose of 1000 mg/m² per 24 hours was administered via intravenous infusion for 120 hours, followed by a 24 hours infusion of NDP at a dose of 100 mg/m² per 24 hours (day 6). During the course of ALCRT, the first course of chemotherapy (with a 25% dose reduction) was administered before RT, and RT (Field A) was then performed for 4 weeks, starting from 3 days after the completion of chemotherapy. The second course of chemotherapy (full-dose) was administered 2 to 3 days after the completion of RT. The second course of RT (Field B) was then administered with a reduced irradiation field 3 days after the second chemotherapy session. The third course of chemotherapy was administered 3 days after the completion of the second course of RT; the dose was reduced by 25% again because of the progression of renal and liver dysfunction after the second chemotherapy and RT sessions. RT was performed with a daily fraction of 1.8 Gy from day 10 to 37 and 2 Gy from day 49 to 71. The initial radiation field covered the area between the left maxilla and the whole left cervical and clavicular region, and RT (36 Gy/20 fractions) was performed using the 3 fields technique for conformal irradiation (Field A). Then, a smaller field was selected for the left maxillary tumor, which was treated with a dose of 34 Gy/17 fractions using the 2 fields technique for conformal irradiation (Field B).

The response to ALCRT was evaluated according to the RECIST (Response Evaluation Criteria in Solid Tumors) guidelines. The tumor reduction effect was considered to represent a partial response. Multiple hypertrophy of the left cervical lymph nodes disappeared, and the strong uptake of FDG in the left cervical lymph nodes also disappeared or normalized. Thus, the effect of ALCRT with regard to lymph node metastasis was considered to represent a complete response. Neck dissection was not performed on this patient.

At approximately 6 months after the first presentation, salvage surgery (extensive Denker's operation) of the residual maxillary tumor was performed to confirm whether any cancer cells remained. A histopathological examination revealed no evidence of residual cancer cells in the surgical specimen.

Finally, the patient has been disease-free for 5 years following the operation. Our patient is quite satisfied with the treatment because of the few side effects, low cosmetic and functional disturbance and complete recovery from the disease. Ethical approval for this report was waived because approval for case

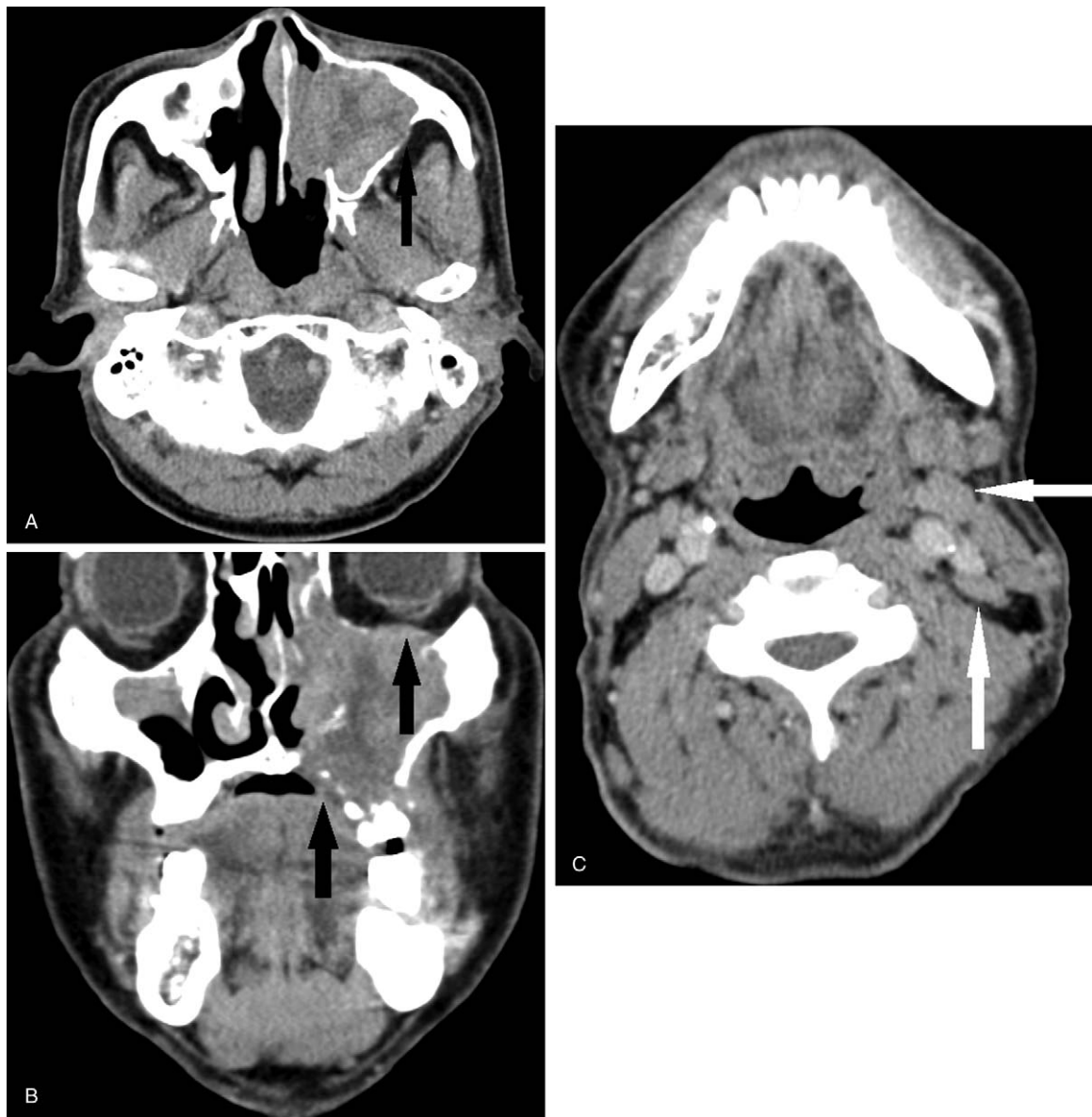


Figure 2. CT images of the present case. A heterogeneously enhanced tumor occupying the left maxillary sinus was found (A, B). The tumor had destroyed and invaded the floor of the left orbit, hard palate and the medial and posterior walls of the left maxillary sinus (black arrow). Left, multiple cervical lymphadenopathies were found (C, white arrow). CT = computed tomography.

reports is not required in our institution. The patient has given informed consent for the publication of this case report.

3. Discussion

3.1. Relationship between LEC and EBV

LEC of the nasopharynx and some other sites have shown a strong association with EBV.^[13] Numerous serologic, immunofluorescence and nucleic acid hybridization studies have strongly linked EBV to NPC. EBER is strongly expressed by the tumor cells in such cases, indicating the presence of EBV RNA. Similarly to NPC, EBV is strongly associated with the pathogenesis of LEC of the sinonasal tract^[12,14]; however, some cases are EBV negative.^[11,15] Sckolnick et al^[3] suggested that the occurrence of LEC in endemic areas, such as Southeast Asia, is associated with

EBV infection. In contrast, LEC is not commonly associated with EBV in Western countries. Our patient was positive for EBER, and it is possible that EBV might have been associated with the occurrence of his left maxillary LEC.

3.2. Clinical characteristics of sinonasal LEC

In 2011, Rytönen et al^[11] reported a literature review of 6 cases of sinonasal LEC, including 1 case in which LEC originated from the nasolacrimal duct. Based on their review, we also reviewed the literature on sinonasal LEC to include studies that were published after 2011 and the present case (Table 1). We excluded cases of LEC originating from the nasolacrimal duct in our review. We found only 8 case reports of sinonasal LEC that included detailed patient information in the English literature from 1980 to 2016.^[2,11,15–20] LEC originating from the

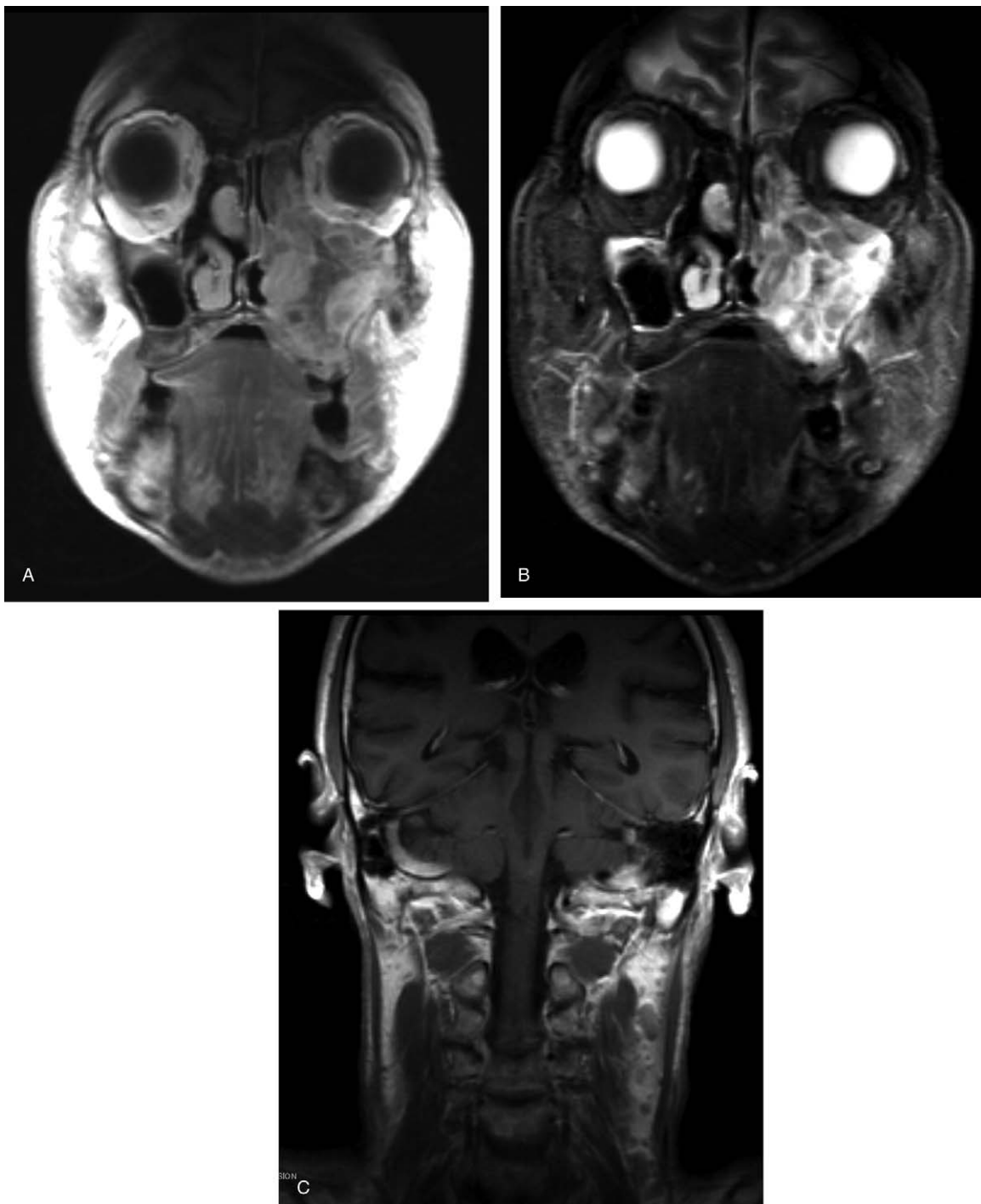


Figure 3. Magnetic resonance images of the present case. Coronal views of enhanced T1-weighted (A) and T2-weighted imaging (B) of the head showed that the tumor occupying the left maxillary sinus had invaded the floor of the left orbit and hard palate, suggesting a malignant tumor. The coronal view of enhanced T1-weighted imaging (C) indicated left cervical lymphadenopathy, suggesting lymph node metastasis.

maxillary sinus occurred in only 4 of the 8 cases.^[2,11,15,16] The mean patient age in these 8 cases was 47.4 (range: 21–72) years; 5 of the patients were men and 3 were women. The clinical symptoms of the patients included epistaxis (n=6; 75.0%), pain or headache (n=4; 50.0%), nasal obstruction (n=4; 50.0%), facial swelling (n=3; 37.5%), and loss of taste and smell (n=1; 12.5%). The tumor sites were the maxillary sinus (n=4), nasal cavity (n=3), and nasal cavity and ethmoid sinus (n=1). The

mean duration of symptoms was 3.0 months. Four of the 8 cases were EBV positive. Cervical lymph node metastasis was not detected in the 8 cases; however, it was detected in our case. Distant metastasis was not found in any of the 8 cases or in our patient. The disease stages of the patients were stage I (n=3), stage II (n=1), stage III (n=3), and stage IV (n=1). The treatment strategies differed between patients with locoregional (stage I/II) and advanced (stage III/IV) disease. Surgical removal was selected

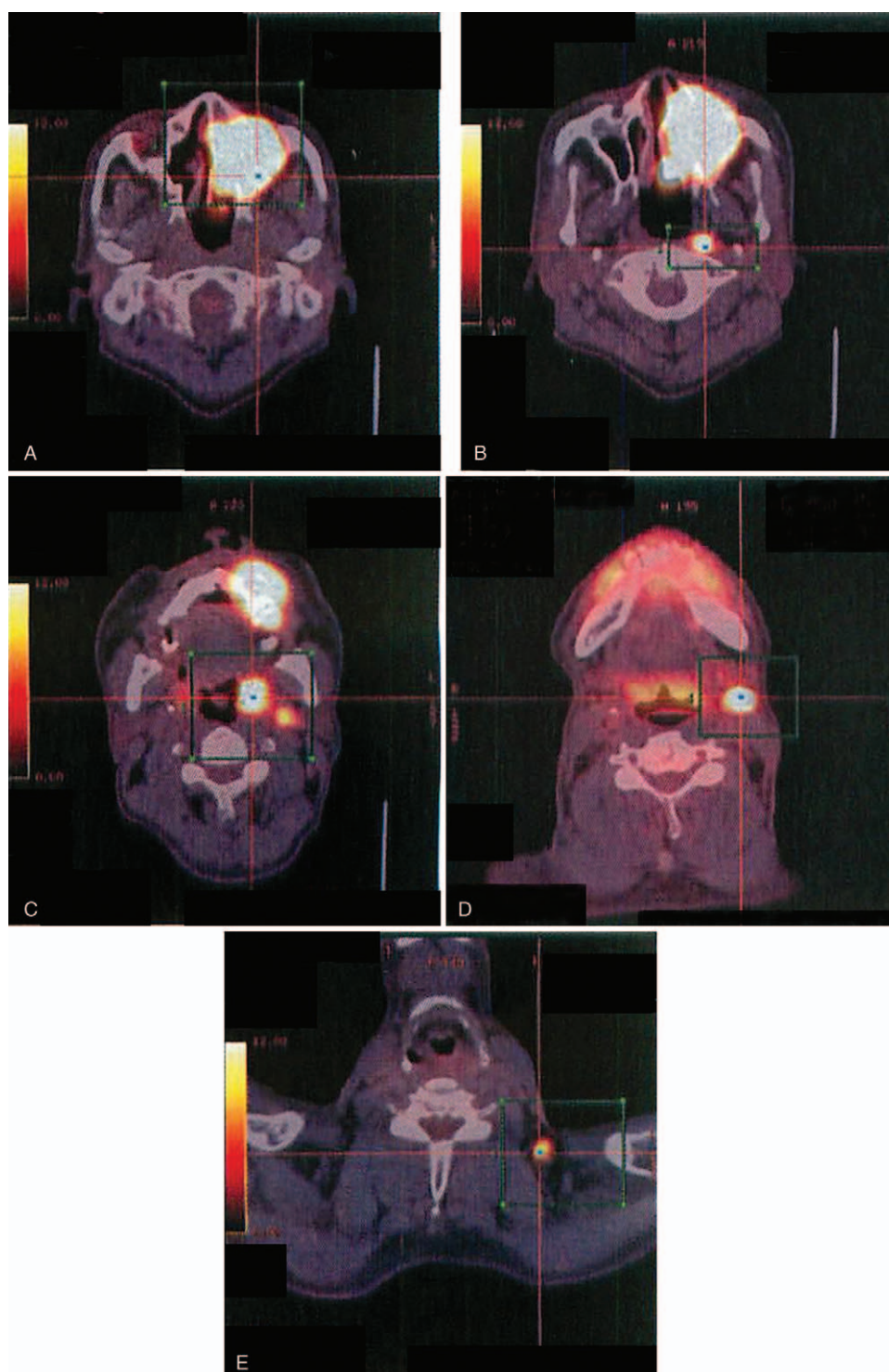


Figure 4. Positron emission tomography (PET) with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG). FDG PET/CT showed strong uptake of FDG in the left maxillary sinus (SUV=37.6) (A), lymph nodes in the left parapharyngeal space (SUV=16.6) (B), left tonsil (SUV=25.6) (C), left submandibular lymph nodes (SUV=17.4) (D), and left supraclavicular lymph nodes (SUV=10.2) (E).

as the initial treatment for all 4 patients with locoregional disease. Radiotherapy and chemoradiotherapy were subsequently performed as postoperative adjuvant therapy for 1 patient and 2 patients, respectively. In contrast, chemoradiotherapy and radiotherapy were selected as the initial treatments for 3 patients and 4 patients with advanced disease, respectively. The mean

follow-up period was 33 (range: 11–36) months, and no relapse or residual tumor was found in any of the 6 patients described in the literature.

The literature contains 2 case series on sinonasal LEC. The authors of both studies belonged to institutions in areas with a high incidence of EBV-positive NPC (Guangzhou and Taipei in

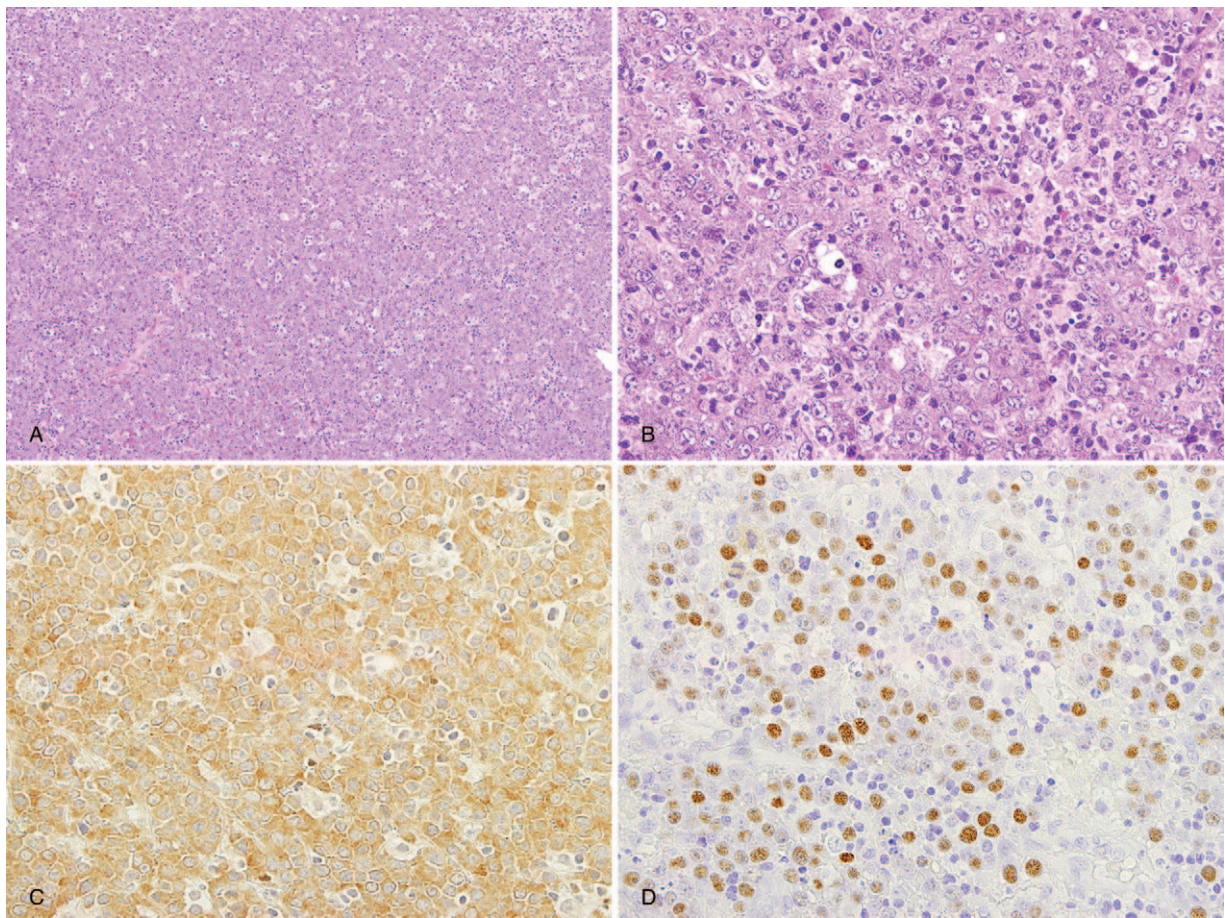


Figure 5. Pathological findings. A, Microscopic view of the lymphoepithelial carcinoma. Tumor cells were arranged in sheets to trabeculae. B, Magnified microscopic view. Tumor cells have large nuclei and prominent nucleoli. Note the lymphocytic infiltrate. C, Tumor cells were immunopositive for CK14. D, In situ hybridization showed the tumor cells to be positive for small EBV-encoded RNA (EBER).

Southeast Asia).^[14,21] Thirty-three patients (all EBV positive) were enrolled in these studies.

Zong et al^[14] reported the pathological characteristics of sinonasal LEC. LEC originating from the maxillary sinus was found in 3 cases (15.0%). Cervical lymph node metastasis was found in 3 of 20 sinonasal LECs (15%), indicating that the frequency of lymph node metastasis in sinonasal LEC was smaller

than that in nasopharyngeal LEC. However, the treatments and the clinical prognoses were not indicated in their report.

Jeng et al^[21] investigated the clinical and histopathological characteristics of primary sinonasal nasopharyngeal-type carcinoma (referred to as sinonasal LEC in the present paper). In their paper, 13 patients (male, n=9; female, n=4) were analyzed. The most common location was the nasal cavity and septum (n=8;

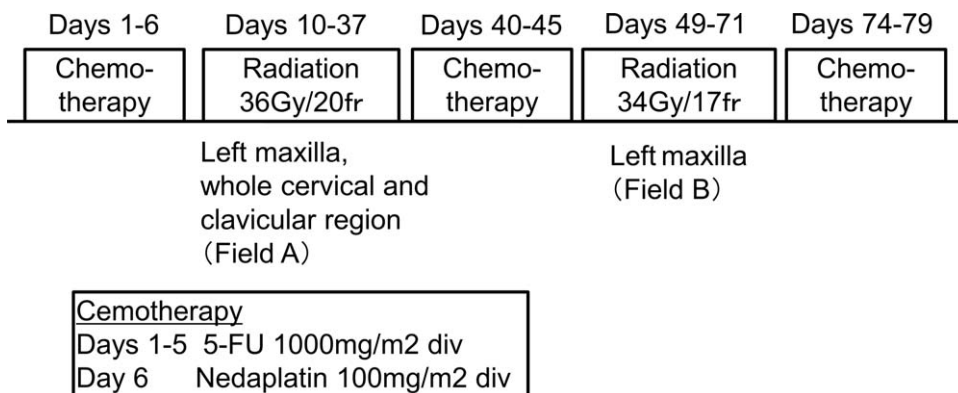


Figure 6. Schematic illustration of the treatment protocol in the present case in which alternating chemoradiotherapy with nedaplatin and 5-FU was performed. 5-FU = 5-fluorouracil.

Table 1**A summary of the review of the literature on sinonasal lymphoepithelial carcinoma (LEC), including the present case.**

Report	Age	Sex	Side	Symptoms	Tumor site/size	Duration of symptoms	Metastases	TMN stage	Treatment	EBV	Follow-up	Relapse or residual
Takakura (2018)	63	M	L	Cheek pain, nasal obstruction and cheek swelling	Maxillary sinus/38 × 48 × 50 mm	17 days	Yes	T3N2bM0 stage IVA	CR⇒S	+	5 yr	No
Muthayam (2014)	45	F	R	Painful swelling of the face, epistaxis	Maxillary sinus/35 × 30 mm	2 mo	No	T3N0M0 stage III	R	–	20 mo	No
Mohammed (2012)	72	F	R	Epistaxis	Maxillary sinus/	3 mo	No	T1N0M0 stage I	S⇒R	–	3 yr	No
Kim (2012)	21	M	R	Nasal stuffiness, epistaxis	Nasal cavity/45 × 21 × 25 mm	4 mo	No	T2N0M0 Stage II	S⇒RC	+	15 mo	No
Rytkönen (2011)	30	M	L	Mild pain and discomfort of the left upper molars, epistaxis	Maxillary sinus/	5 mo	No	T2N0M0 stage II	S⇒RC	–	11 mo	No
Trabelsi (2010)	58	M	L	Nasal obstruction, epistaxis	Nasal septum/30 × 50 mm	2 mo	No	T3N0M0 stage III	CR ⇒S (neck)	+	12 mo	No
Jung (2009)	64	F	R	Swelling on the right side of the face	Maxillary sinus/5 × 5 cm	3 mo	No	T3N0M0 stage III	S⇒R⇒C	–	36 mo	No
Hajjioannou (2006)	33	M	R	Headache, persistent nasal congestion, loss of smell and taste, epistaxis	Nasal cavity, ethmoid sinus/	2 mo	No	T4bN0M0 stage IVB	CR	+	n/a	n/a
Wöckel (1986)	56	M	R	n/a	Meatus of nose/	n/a	No	T1N0M0 stage I	S	+	n/a	n/a

A summary of the review of the literature on sinonasal lymphoepithelial carcinoma (LEC), including the present case.

– = negative, + = positive, C = chemotherapy, EBV = Epstein–Barr virus, F = female, mo = months, M = male, n/a = not available, R = radiotherapy, S = surgery, yr = years.

61.5%). In 5 cases, the tumors were located in the maxillary sinus (38.5%). Orbital and intracranial invasion was seen in 4 (31%) and 2 (15%) cases, and cervical node metastasis was detected in 3 cases (23%). Distant metastasis to the bone and other sites was only detected in 1 case. The treatments included radiotherapy (n=10) and surgical resection (n=7). Chemotherapy was administered to 3 patients. Two patients died of disease at 7 and 62 months, respectively, after the diagnosis. Eight patients (61%) were disease free at their last follow-up examination (median follow-up time: 48 months).

3.3. Treatment for sinonasal LEC

A standard treatment approach for sinonasal LEC has not been established because of the rarity of reported cases. Non-nasopharyngeal LEC of the head and neck is a highly radiosensitive disease for which excellent local control rates can be achieved with radiotherapy.^[22] Dubey et al^[22] suggested that radiotherapy is an appropriate initial locoregional therapy for patients with this disease. They recommended systemic therapy with chemotherapy for non-nasopharyngeal LEC patients who present with regional adenopathy because they have a relatively high rate of distant metastasis. Furthermore, they suggested that surgery should be reserved for patients who have persistent disease after the completion of radiotherapy.^[22]

ALCRT is a minor variation of concurrent chemoradiation aimed at minimizing toxicity.^[23] In Japan, ALCRT with 3 courses of chemotherapy, consisting of 5-FU and CDDP, and 2 courses of radiotherapy, which are sandwiched with the chemotherapy, has been used for the treatment of locoregional advanced NPC in many institutions.^[24] This method of ALCRT yielded higher or at least similar survival rates and lower toxicities in comparison with concurrent chemoradiation for NPC.^[24] The 5-year overall survival and progression-free survival rates were 78.04% (95% CI: 69.1%–87.0%), and 68.74% (95% CI: 58.8%–78.7%), respectively.^[24] NDP, a derivative of CDDP that was developed in Japan, was used in our patient to avoid the renal dysfunction that may develop in association with the administration of CDDP. This antitumor agent has shown promising activity in cervical cancer and is associated with less renal and gastrointestinal toxicity.^[25] Previous studies have

indicated that ALCRT with 5-FU and NDP was feasible and effective for patients with head and neck cancer,^[26] esophageal cancer,^[27] and advanced cervical carcinoma.^[25]

The tumor in our patient invaded the left orbit and hard palate. If surgical removal had been selected as the initial treatment, we would have had to select total maxillectomy, and the patient might have suffered cosmetic and functional disturbance due to the loss of the left eye and hard palate. Thus, we selected ALCRT with 5-FU and NDP as the initial treatment, followed by salvage surgery for the residual tumor, out of consideration for the patient's quality of life and treatment results. Treatment resulted in partial response of the regional tumor and complete response of the cervical lymph node metastasis, and pathological complete response of the regional tumor was confirmed by salvage surgery. Mild renal dysfunction occurred during ALCRT with NDP, but the patient recovered after the NDP dose was reduced. Our patient could complete the ALCRT regimen without a break and ultimately has been disease free for 5 years. We believe that ALCRT with 5-FU and NDP followed by salvage surgery is one of the most effective treatments for LEC of the sinonasal tract from the viewpoint of balancing the quality of life with high curative effect.

4. Conclusion

We treated an extremely rare case of LEC of the left maxillary sinus that invaded the left orbit and hard palate with cervical lymph node metastasis. Five-year disease-free survival was achieved without cosmetic or functional disturbance. To our knowledge, this is the first case of LEC of the maxillary sinus treated with ALCRT followed by salvage surgery, which can be expected to have a high curative effect with few side effects.

Author contributions

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Visualization: Takahiko Nakajima.

Writing – original draft: Hiromasa Takakura.

Writing – review & editing: Hideo Shojaku.

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