Case Report

Epstein-Barr Virus-Negative Associated with Sinonasal Lymphoepithelial Carcinoma –A Rare Case Report

Mohamad Najib Salleh[1,2], Nurul Syuhadah Hasny[1], Ramiza Ramza Ramli[1], Sakinah Mohamad[1], Norasnieda Md Shukri[1], Nusaibah Azman[3], Faezahtul Arbaeyah Hussain[3]

Abstract

Lymphoepithelial carcinoma (LEC), also known as lymphoepithelioma-like carcinoma, is a rare type of cancer. LEC can affect any organ, but it is most common in the head and neck region. Sinonasal lymphoepithelial carcinoma (SNLEC) is an example of LEC that can occur in our body and it is very rare. LEC has usually associated with Epstein-Barr virus (EBV) infection and gives a picture of undifferentiated carcinoma with an intermixed reactive lymphoplasmacytic infiltrate on histology. It is pretty difficult to commit to a diagnosis, therefore histological examination and immunohistochemical investigations are used to determine the ultimate definite diagnosis. Most cases present with locally aggressive illness, which may or may not include regional lymph node metastases. General treatment depends on the patient's condition, including surgical resection, radiation therapy, and chemotherapy. Herein, we present a case of a young, previously healthy gentleman with sudden onset of anosmia with left eye blurred vision whose final diagnosis was EBV negative SNLEC subsequently managed by radiotherapy.

Keywords: Lymphoepithelial carcinoma; anosmia; sinonasal; radiotherapy; histology

International Journal of Human and Health Sciences Vol. 07 No. 01 January'23 Page : 89-94
DOI: http://dx.doi.org/10.31344/ijhhs.v7i1.504

Introduction

Schminke and Regaud first described LEC in 1921 [1]. LEC is commonly found in the nasopharynx, salivary glands, and larynx in the head and neck region. However, it is relatively uncommon in the sinonasal area compared to other malignant lesions. SNLEC is rare cancer with only about 40 occurrences reported, and over 90% of lesions positive for the Epstein-Barr virus (EBV). SLEC is found throughout the world; however, it is more prevalent in Southeast Asia.[1] Nests, sheets, or individual undifferentiated or poorly differentiated malignant epithelial cells surrounded and penetrated by substantial components of small, mature lymphocytes and plasma cells are microscopic descriptions of LEC.[2] Patients are usually asymptomatic but may present as non-specific symptoms depending on the location of the lesion, and sometimes the lesion is discovered by coincidence during imaging. In our case, the patient initially complained of anosmia only and later on developed eye symptoms after disease progression. Clinicoradiological tests, in general, do not help identify the ultimate diagnosis. The conclusive diagnosis of LEC is made using histology and immunohistochemistry tests.[2] Thus, in this case report, we present a case of SNLEC and the management experience of our patient

1. Department of Otorhinolaryngology-Head & Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kota Bharu, Kelantan, Malaysia.
2. Department of Otorhinolaryngology-Head and Neck Surgery, Hospital Tuanku Fauziah, Kangar, Perlis, Malaysia.
3. Department of Pathology, School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kota Bharu, Kelantan, Malaysia.

Correspondence to: Dr. Ramiza Ramza Ramli, Department of Otorhinolaryngology-Head & Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kota Bharu, Kelantan, Malaysia. Email: ramizaramza@usm.my

Case Report

A 39-year-old Malay man with no previous medical illness presented with a loss of smell that had been present for the past three months, which was sudden onset and persistently associated with intermittent loss of taste. Besides that, he also had rhinitis symptoms since young, like occasional rhinorrhea, sneezing, nasal itchiness and bilateral nasal blockage, which were aggravated by dust and seafood. Otherwise, he never experienced epistaxis, foul smelly nasal discharge, posterior nasal drip, facial pain, headache, limb weakness, eye or ear pain, or diplopia. There was no history of trauma, no loss of weight or appetite, no night sweat or tuberculosis bacilli contact or symptoms like night sweat, chronic cough or hemoptysis. He works as a medical assistant at a governmental hospital and has no exposure to wood dust, fume or inhalation injury. For the initial presentation, the patient sought treatment at Otorhinolaryngology (ORL) clinic; that clinical examination showed no facial deformities, no mass on anterior rhinoscopy, and a normal cold spatula test nasoendoscopy showed left deviated septum with no apparent mass seen. The doctor treated it for allergic rhinitis with the deviated nasal septum. Rapid Test Kit antigen (RTK-Ag) for coronavirus was also done twice shown negative results. Then patient complained of the painless left lower eyelid swelling that was present for one month that extended into the medial canthus and superolateral to the eye globe associated with decreased vision over the left eye for one week; thus, he then sought treatment at the ophthalmology clinic. Otherwise, patient had no nasal swelling or deformity, no headache, no vomiting altered level of consciousness.Due to anosmia and suddenly associated with eye swelling, the ophthalmology team proceeded with an urgent Computed Tomography Scan (CT) of the brain, orbit and paranasal sinus to look for any relevant findings to suggest the cause of the manifestation.From the CT scan, the image showed the presence of heterogeneously enhancing soft tissue mass occupying the ethmoid air cells measuring approximately 5.6 x 3.4 x 4.6cm (APxWxCC), destruction of the frontal bone, posterior wall of the frontal sinus and cribriform plate with the extension of the mass to the frontal sinus. The mass extends into the anterior cranial fossa, causing the frontal lobe's mass effect and causing bony destruction of the bilateral lamina papyracea and left optic canal (Figure 1A & 1B). The working diagnosis was aggressive paranasal soft tissue mass with extensive bony destruction, and intracranial extension may represent esthesioneuroblastoma or sinonasal carcinoma that need tissue biopsy to establish the diagnosis.

The case then was referred to our centre for further assessment. Upon initial inspection, we did a thorough clinical examination. Examination showed left periorbital swelling and proptosis with impaired cranial nerve I, II, VI of the left side (Figure 2).Nasoendoscopy showed left septal spur touching the inferior turbinate, high left deviated nasal septum touching the middle turbinate, congested left lateral nasal wall, mucoid discharge seen at the left middle meatus, olfactory cleft and bilateral Fossa of Rosenmuller was clearwith no noticeable nasal mass or polyp seen. Otherwise, no other abnormalities were detected in the ear, intraoral, and neck examination.

We proceeded with examination under anaesthesia because of no noticeable nasal mass seen via nasoendocopy in our clinic as a CT scan has shown aggressive soft tissue mass with extensive bony destruction. During intra-operation, after done uncinectomy,we noted a fleshy mass occupying the middle meatus and a biopsy was taken and sent for a histopathology examination (Figure 3). After a thorough histopathology examination, the result came back as LEC EBV negative (Figure 4). Histopathology examination showed tumour cells arranged in sheets and nests separated by hyalinised stroma and minimal intervening lymphocytic infiltrates. The nuclei were enlarged, round to oval with vesicular chromatin and occasional prominent nucleoli. Mitoses are hardly seen. Immunohistochemical study showed tumour cells were positive for high molecular weight cytokeratin marker, CK5/6 and p63, while low molecular weight cytokeratin marker CK7 was negative. This biopsy showed sparse lymphocytic infiltrates as shown by CD3 (T cell marker) and CD20 (B cell marker). Tumour cells are also negative for p16 and synaptophysin. We have outsourced for EBER in-situ hybridization, which was reported as negative.

After a multidisciplinary team discussion, we decided for the patient to undergo chemotherapy followed by radiotherapy, as the patient's staging prior to treatment was T4bN0Mx. Currently, patients under the oncology team follow up for completion of treatment.

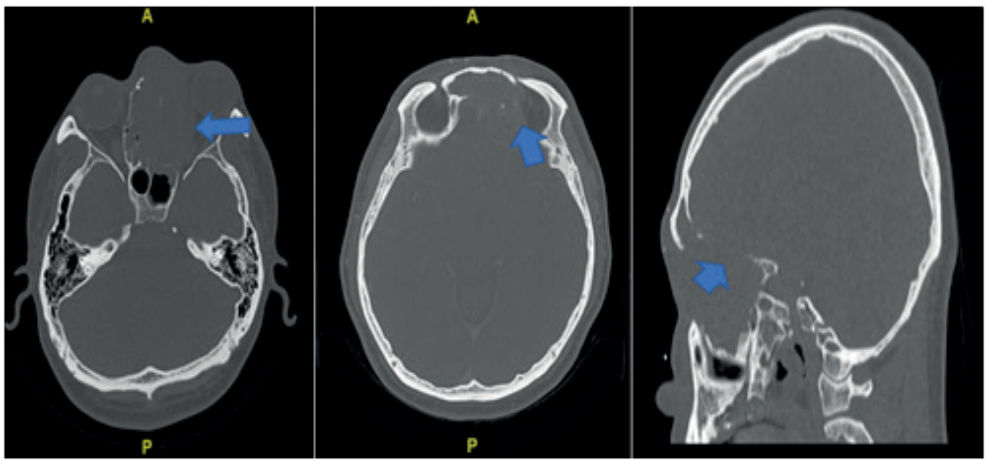

Figure 1A: CT scan bone setting axial and sagittal view shown mass over ethmoid sinus caused the destruction of the frontal bone, posterior wall of the frontal sinus and cribriform plate with the extension of the mass to the frontal sinus and also causes bony destruction of the bilateral lamina papyracea and left optic canal;

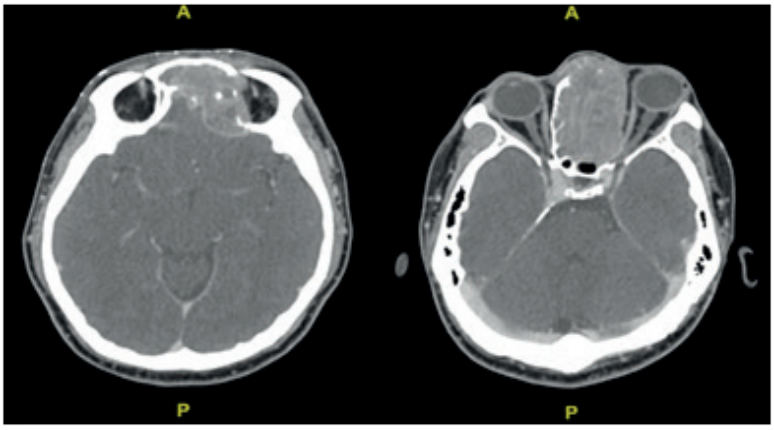

Figure 1B: CT scan soft tissue setting was shown to be of heterogeneously enhancing soft tissue mass occupying the ethmoid air cells extend to the frontal sinus and had intracranial extension into the anterior cranial fossa, causing a mass effect to the frontal lobe.

Figure 2. The noted patient had obvious left periorbital swelling and left eye proptosis during the examination.

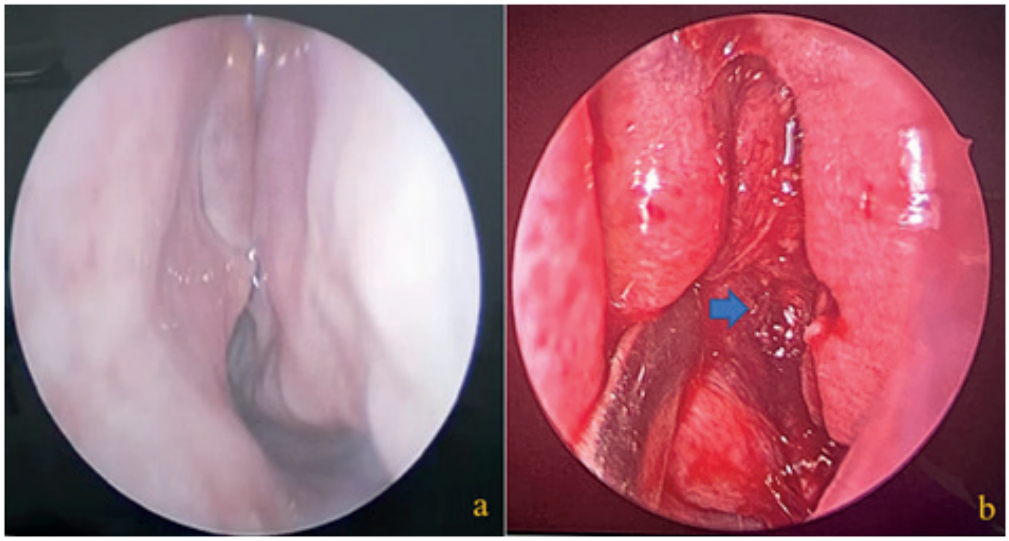

Figure 3: a) Nasal endoscopy showed no apparent mass seen before we proceeded with examinaton under anaesthesia. Biopsy was taken and sent for a histopathology examination;b) shows fleshy mass seen after the uncinectomy over the lateral wall of the nasal cavity.

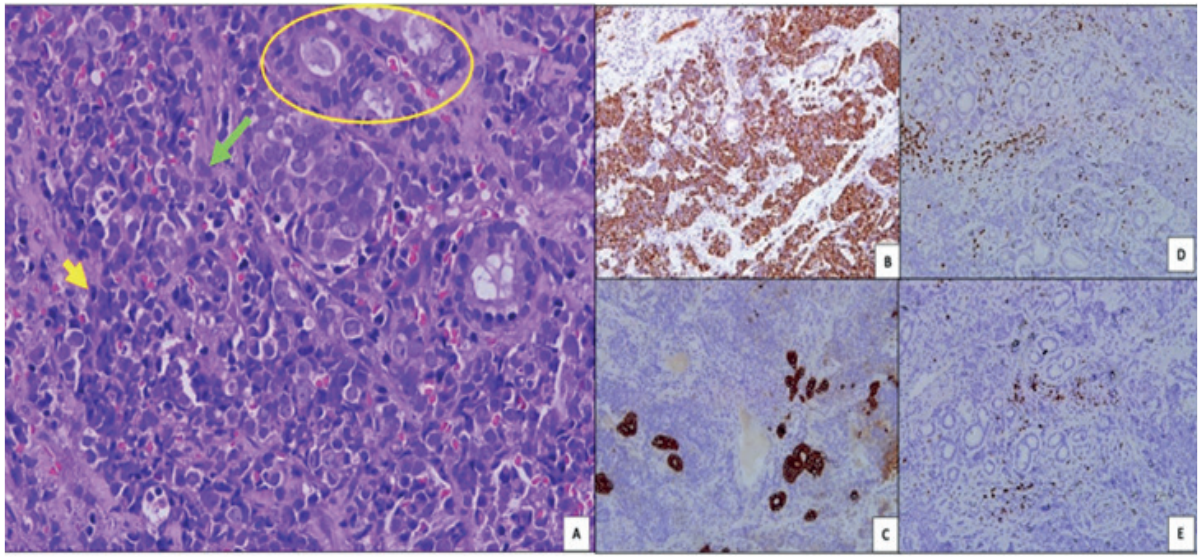

Figure 4:(**A**) Tissue from the middle meatus lesion (H&E, ×400)showing tumour cells arranged in clusters (green arrow) with minimal lymphocyte infiltrates (yellow arrow). Adjacent normal glands are seen (yellow circles). The tumour cells are strongly positive for CK5/6 (**B**, ×100), negative for CK7 (**C**, ×40) both are carcinoma markers, and CD3 (**D**, ×40) & CD20 (**E**,×40) are markers for T and B lymphoid cells are minimally seen scattered in between the tumour cells.

Discussion

LEC is defined by the World Health Organization (WHO) as "a poorly differentiated squamous cell carcinoma or histologically undifferentiated carcinoma with a prominent reactive lymphoplasmacytic infiltrate, morphologically similar to nasopharyngeal carcinoma and there is no keratinization, necrosis, or mucus production.[3]The nasopharynx, salivary glands, and larynx are all common sites for LEC. The lungs, oesophagus, stomach, pancreas, skin, cervix, endometrial, vulva, kidney, bladder, and central nervous system are rarely affected.[3] LEC is most usually diagnosed in people between the ages of 40 to 70,[4] like in our case; the patient was 39 years old. The EBV was found in 87.5 % of all LEC cases, while the remainder is EBV negative.

EBV appears to play a function in the aetiology of LEC depending on the anatomical site [1,4]. The absence of EBV does not exclude the diagnosis. Oral and oropharyngeal LECs are more likely to metastasize (70%) and spread locally (16.6%), whereas nasal and paranasal LECs are less likely to metastasize (60%) and disseminate locally.[1,4]The patient is usually asymptomatic in most cases, but the patient can present depending on the lesion's location. For example, if it occurs in the sinonasal area, it may present with nasal symptoms such as nose block, nasal discharge, altered smell, and rarely cause bleeding.[2] Sometimes the lesion is discovered accidentally during imaging. The sinonasal LEC, as well as specific other sites, have shown a solid link with EBV. EBV has been highly related to nasopharyngeal carcinoma (NPC) in numerous serologic, immunofluorescence, and nucleic acid hybridisation studies. EBV is significantly linked to the aetiology of LEC of the sinonasal tract, similar to NPC, but some instances are EBV negative. In such circumstances, tumour cells express high levels of EBV RNA, which can be detected in the EBER in-situ hybridisation test.

EBER in-situ hybridisation test helps differentiate between LEC and sinonasal undifferentiated carcinoma (SNUC), in which SNUC is consistently EBER-negative. There are very few reported LEC cases with EBV negative.[1] Differentials of LEC include lymphoma, melanoma, olfactory neuroblastomaand sinonasal undifferentiated carcinoma (SNUC). The latter lack syncytial growth pattern and has more profound necrosis and mitoses.Immunohistochemically, it lacks CK5/6 and is limited to absent p63.[1,5]

All sinonasal tumours are equally detectable on CT and MRI. MRI performed better than CT in detecting tumour margin and extension of the tumour, thus can help in making a diagnosis and preparation for planning surgery and providing an operative road map for subsequent functional endoscopic sinus surgery. Still, it cannot give a definitive diagnosis compared to histological examination and immunohistochemical investigations.[6] Patients with LEC of head and neck with regional invasion have a high chance for distal metastases. In Dubey et al.[7], the 5-year actuarial rate of distant metastasis in patients who presented with lymphadenopathywas 36%, and the incidence of regional adenopathy at the time of diagnosis was 76%. Previous studies have shown that nasopharyngeal LEC is a radiosensitive condition for which radiation can achieve excellent local control rates.[7-9] Radiotherapy should be the primary treatment modality even for cases with lymph node metastasis.[9] Locoregional treatment strategy for patients with non-nasopharyngeal LEC will be to irradiate all the primary tumours. Excellent local control rates can be achieved using widely differing fractionation schemes.[7]The 5-year overall survival and progression-free survival rates were 78.04% and 68.74%, respectively.[10]

Conclusion

SNLEC is a very rare malignant tumourwith limited discussion in the literature and has features of rapid disease progressiveness. The symptoms of LEC might vary depending on the location of the lesion. Making a diagnosis is highly complex and time-consuming. However, CT or MRI is an essential tool for assessing lesions to look for extension, depth, and structure related, thus can narrow the differential diagnosis. Histopathological examination and immunohistochemistry studies are used to make the final diagnosis.Early diagnosis and treatment are mandatory because LEC is highly radiosensitive and has a good outcome if treated early.

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical issue: Informed consent was obtained from the patient for publication of this case report and any accompanying images.

Authors' Contribution: Study conception and design, acquisition of data: MNS, NSH; Analysis and interpretation of data,drafting of the manuscript, critical revision: MNS, NSH, RRR, SM, NMS, NA, FAH.

References:

1. Bonnerup S, Gitau M, Shafique K. A Rare Case of Sinonasal Lymphoepithelial Carcinoma Presented With Clinically Stage IV Disease. Ear Nose Throat J. 2022;101(6):386-91.
2. Mohammed D, Jaber A, Philippe M, Kishore S. Lymphoepithelial carcinoma in the maxillary sinus: a case report. J Med Case Rep. 2012;6:416.
3. Rytkönen AE, Hirvikoski PP, Salo TA. Lymphoepithelial carcinoma: two case reports and a systematic review of oral and sinonasal cases. Head Neck Pathol. 2011;5(4):327-34.
4. Almeida LY, Silveira HA, Silva EV, Barbeiro CO, de Paula JA, Bufalino A, Ribeiro-Silva A, León JE. EBV-negative lymphoepithelial-like carcinoma of the lower lip. Autops Case Rep. 2019;10(1):e2020138.
5. Wenig BM. Lymphoepithelial-like carcinomas of the head and neck. Semin DiagnPathol. 2015;32(1):74-86.
6. Gomaa MA, Hammad MS, Abdelmoghny A, Elsherif AM, Tawfik HM. Magnetic resonance imaging versus computed tomography and different imaging modalities in evaluation of sinonasal neoplasms diagnosed by histopathology. Clin Med Insights Ear Nose Throat. 2013;6:9-15.
7. Dubey P, Ha CS, Ang KK, El-Naggar AK, Knapp C, Byers RM, Morrison WH. Nonnasopharyngeal lymphoepithelioma of the head and neck. Cancer. 1998;82(8):1556-62.
8. Sanguineti G, Geara FB, Garden AS, Tucker SL, Ang KK, Morrison WH, Peters LJ. Carcinoma of the nasopharynx treated by radiotherapy alone: determinants of local and regional control. Int J Radiat Oncol Biol Phys. 1997;37(5):985-96.
9. Allen MW, Schwartz DL, Rana V, Adapala P, Morrison WH, Hanna EY, Weber RS, Garden AS, Ang KK. Long-term radiotherapy outcomes for nasal cavity and septal cancers. Int J Radiat Oncol Biol Phys. 2008;71(2):401-6.
10. Takakura H, Tachino H, Fujisaka M, Nakajima T, Yamagishi K, Ishida M, Shojaku H. Lymphoepithelial carcinoma of the maxillary sinus: A case report and review of the literature. Medicine (Baltimore). 2018;97(28):e11371.