Primary lymphoepithelial carcinoma of the hypopharynx: an extremely rare non-nasopharyngeal presentation

Pierwotny nabłoniak chłonny gardła dolnego: niezwykle rzadka prezentacja pozanosogardłowa

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ABSTRACT:

Introduction: A 66-year-old male complained of throat discomfort and odynophagia. Laryngeal fiber optic examination was normal but narrow band imaging was suspicious. USG-FNAC from a cervical lymph node was positive for malignant metastatic carcinoma cells. CECT revealed obliteration of the left pyriform fossa till the level of cricoid cartilage, abutting the ala of the thyroid cartilage, arytenoid cartilage and prevertebral muscles. UGIE revealed an ulcerated mass lesion in the left pyriform fossa. Histopathological examination revealed stratified non-keratinized squamous epithelial lined tissue with subepithelial stroma showing large round to polygonal tumour cells. The tumour cells were surrounded by a lymphoid stroma. On immunohistochemistry the tumour cells were positive for pancytokeratin and negative for CD45, chromogranin and synaptophysin. Lymphocytes were positive for CD45. The diagnosis of lymphoepithelial carcinoma was established. The tumour was inoperable and was treated by radiotherapy.

Conclusions: Lymphoepithelial carcinoma is the primary entity of the nasopharynx but rarely seen at sites like oropharynx, larynx and hypopharynx. Only around 50 non-nasopharyngeal cases have been reported till date out of which only 10–12 were in the hypopharynx. Radiotherapy is the mainstay of treatment whereas surgery can be considered for a local disease.

KEYWORDS: Epstein-Barr virus, laryngopharynx lymphoepithelioma, larynx, LEC, pyriform sinus

STRESZCZENIE:

Wstęp: 66-letni mężczyzna uskarżał się na dyskomfort gardła i ból przy przełykaniu. Wynik badania fiberoskopowego krtani był prawidłowy, natomiast podejrzenia budził obraz uzyskany z użyciem wąskiej wiązki obrazowania. Uzyskano dodatni wynik badania USG-FNAC pod kątem obecności złośliwych, przerzutowych komórek rakowych. W badaniu tomografii komputerowej szyi z kontrastem uwidoczniono zatarcie lewego zachyłka gruszkowatego do poziomu chrząstki pierścieniowatej, stykające się ze skrzydłami chrząstki tarczowatej, chrząstką nalewkowatą i mięśniami przedkręgowymi. W badaniu endoskopowym GOPP ujawniono obecność owrzodzonej masy w lewym zachyłku gruszkowatym. Badanie histopatologiczne wykazało obecność stratyfikowanej, wyścielonej niezrogowaciałym nabłonkiem płaskokomórkowym tkanki z dużymi kolistymi lub wielokątnymi komórkami nowotworowymi widocznymi w zrębie podnabłonkowym. Komórki nowotworowe były otoczone zrębem limfatycznym. W badaniu immunohistochemicznym komórki nowotworowe dały wynik dodatni dla pancytokeratyny i ujemny dla: CD45, chromograniny i synaptofizyny. Limfocyty dały wynik dodatni dla CD45. Postawiono rozpoznanie raka limfonabłonkowego. Ze względu na nieoperacyjność guza w leczeniu, zastosowano radioterapię.

Wnioski: Nabłoniak chłonny jest pierwotnym guzem nosogardzieli, lecz rzadko obserwuje się go w miejscach, takich jak: gardło środkowe, krtań i gardło dolne. Do dzisiaj zgłoszono jedynie około 50 przypadków pozanosogardłowych, w tym jedynie 10–12 zlokalizowanych w gardle dolnym. Podstawą leczenia jest radioterapia, choć w przypadkach zmian miejscowych można rozważać operację chirurgiczną.

SŁOWA KLUCZOWE: nabłoniak chłonny części krtaniowej gardła, LEC, wirus Epsteina-Barr, zachyłek gruszkowaty

ABBREVIATIONS

BAL – broncho-alveolar lavage
CECT – contrast-enhanced computed tomography
EBV – Epstein-Barr virus
FDG – fluorodeoxyglucose
HNSCC – Head and neck squamous cell carcinoma
HPE – histopathological examination

IHC – immunohistochemistry
IPCL – intra-papillary capillary loop
LEC – lymphoepithelial carcinoma
LMP-1 – anti-latent membrane protein 1
PET – positron emission tomography
RT – radiotherapy
SCC – squamous cell carcinoma
UGIE – upper gastrointestinal endoscopy

INTRODUCTION

Lymphoepithelial carcinoma (LEC) also known as lymphoepithelioma is a squamous cell carcinoma associated with lymphoid stroma. This tumour occurs worldwide and is seen endemically in Southeast Asia and in Eskimos [1]. LEC is a rare presentation in the head and neck region. Till date, only around 50 cases have been reported in English literature. This is the primary entity of the nasopharynx but rarely seen at other sites, like sinonasal tract, nasolacrimal tract, oropharynx, larynx, major salivary glands, oral cavity, hypopharynx, thymus, esophagus, trachea, lungs and stomach [2].

It is categorized as undifferentiated squamous cell carcinoma (WHO type 3) variant of nasopharyngeal neoplasm [3]. It accounts for only 0.2% of all laryngeal tumours [4]. Squamous cell carcinoma of the larynx and adjoining areas is easy to diagnose as most of these cases show ulceration, bulge or fungation whereas LEC is more of a submucosal growth which mostly presents as an innocuous smooth growth appearing normal on examination initially which is difficult to diagnose until symptoms have progressed. Most of the cases present with cervical lymphadenopathy and dysphagia or rarely dyspnea depending on the area of presentation. As the non-nasopharyngeal presentations are so rare, the clinical course, diagnosis and treatment for this tumour are not well recorded and described. Lymphoepithelial carcinoma of the hypopharynx was first described by Dockarty et al. in 1968 and then by Ferlito et al. in 1977 [5]. It is of very rare occurrence and there are only around 10–12 reported cases as searched online by the authors. Radiotherapy is supposed to be the treatment of choice for these patients [6, 7]. We hereby report a case and discuss the clinical and histopathological findings, the diagnostic problems and management of this rare neoplasm based on very little information available for reference.

Permission was taken from the Institutional Ethics Committee for publishing the case report before preparing the manuscript. Proper written informed consent in vernacular language was taken from the patient to use the images and history for publication purposes.

CASE REPORT

A 66-year-old Indian male presented to the otorhinolaryngological outpatient department of our institute with a complaint of progressively increasing throat discomfort and pain during swallowing for the last 1 year. Patient's documentation revealed that he was investigated at another medical center at the time of commencement

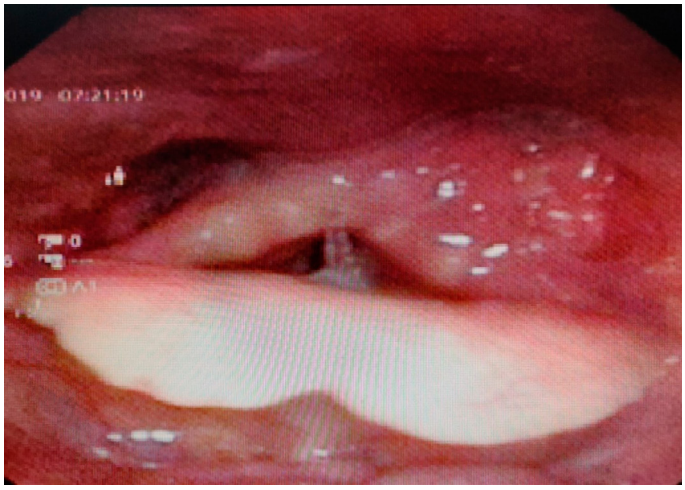

Fig. 1. White light fiber optic laryngoscopy showing a smooth bulge in the left pyriform fossa.

of symptoms where a direct laryngoscopic examination was carried out and a small smooth bulge was noticed in the left pyriform fossa. A biopsy was taken and its result was inconclusive. In repeat biopsy, there was a suspicion of poorly differentiated malignancy, and thus immunohistochemistry (IHC) was advised for a definitive diagnosis along with a positron emission tomography (PET). The PET scan revealed a fluoro-deoxyglucose (FDG) avid enhancing ill-defined soft tissue thickening in the region of the left pyriform fossa along with non-FDG avid sub-centimeter-sized bilateral level IB, II and III cervical lymph nodes. FDG avid mediastinal lymph nodes showing calcifications in the right hilar region were also seen along with minimal pleural effusion on the left side with faintly FDG avid, small areas of subpleural consolidation of the left lower lobe. Bronchoscopy was done and bronchoalveolar lavage (BAL) taken for malignant cells which came out to be negative. The patient was called for further follow-up. However, as his pain relieved, he did not turn up for further investigations. The patient had then approached our outpatient department when his symptoms reappeared and were progressively worsening over the last 4 months. He also complained of slight difficulty in breathing. His history revealed he was a non-smoker, non-tobacco user and non-drinker. Any other medical history was negative except for diabetic profile.

Contrast-enhanced computed tomography (CECT) of the neck revealed obliteration of the left pyriform fossa by heterogeneous enhancing soft tissue extending till the level of the upper margin of the cricoid cartilage, measuring 3.3 cm x 1.9 cm x 1.9 cm. Antero-laterally it was abutting the ala of the thyroid cartilage, antero-medially abutting the arytenoid cartilage and posteriorly abutting the prevertebral muscles. Thorax CECT revealed the evidence of focal areas of fibrosis involving the peripheral aspect of the left upper and lower lobes with subtle areas of fibrosis in the right upper lobe. Few enlarged lymph nodes were seen in mediastinum.

White light laryngeal fiber optic examination was performed which showed congestion in the left pyriform fossa but on narrow band imaging IPCL grade 3 capillary pattern [8] was seen in the left pyriform fossa. Biopsy was taken from the suspicious area at the same time but it came out to be inconclusive.

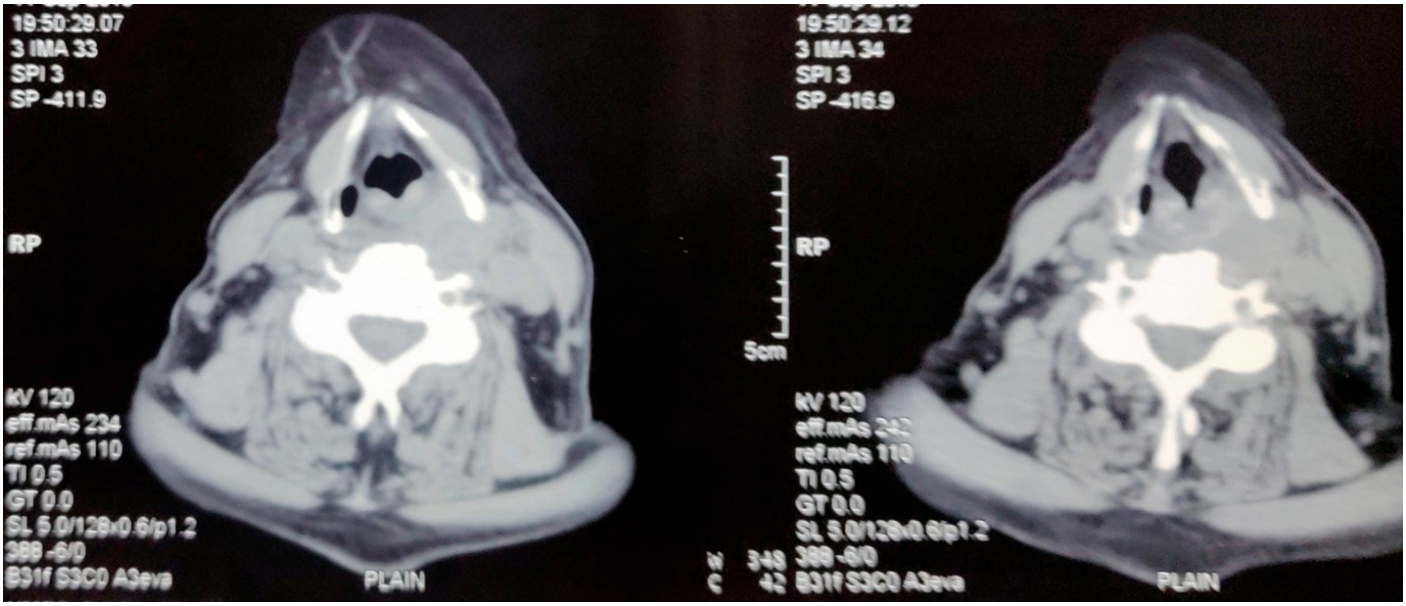

Fig. 2. Neck CECT showing growth in the left pyriform fossa.

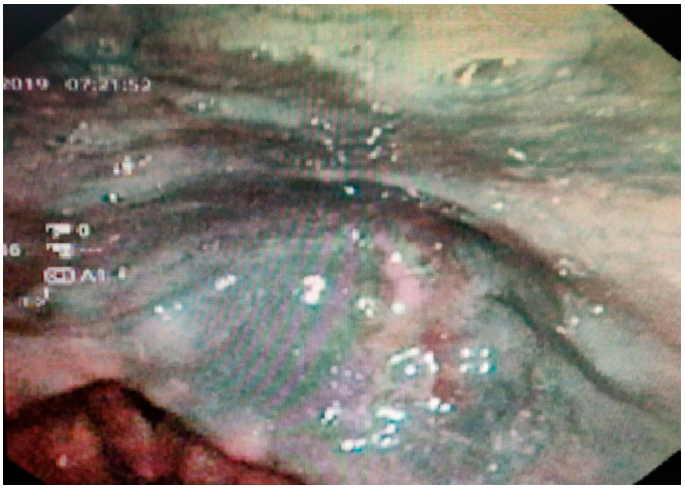

Fig. 3. Narrow Band Imaging showing suspicious intra-papillary capillary loop (IPCL) vascular pattern in the left pyriform fossa.

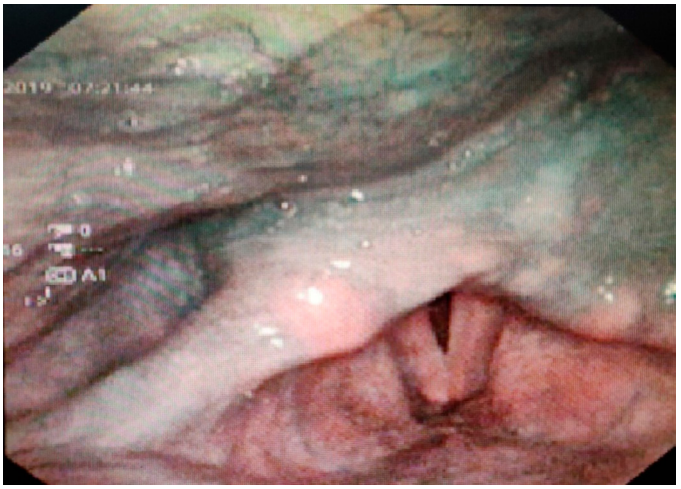

Fig. 4. Narrow Band Imaging showing normal IPCL vascular pattern in the right pyriform fossa.

Ultrasound-guided fine needle aspiration cytology was taken from a left-side 1.3 cm x 0.8 cm level II cervical lymph node which came positive for malignant cells suggestive of metastatic carcinoma. As previous attempts of direct laryngoscopic examination and biopsy did not form any conclusive diagnosis, upper gastrointestinal endoscopy (UGIE) was planned to evaluate hidden involved areas of the hypopharynx not accessible by a rigid laryngoscope. UGIE revealed an ulcerated mass lesion in the deeper region of the apex of the left pyriform fossa along with a large hiatus hernia. Multiple biopsies were taken from the lesion and sent for histopathological examination (HPE).

HPE revealed stratified non-keratinized squamous epithelial lined tissue with sub-epithelial stroma showing large round to polygonal tumour cells intimately admixed with small lymphocytes. The tumour cells displayed moderately pleomorphic hyperchromatic nuclei, conspicuous nucleoli in places and eosinophilic cytoplasm with indistinct cell borders.

On immunohistochemistry the tumour cells were positive for pancytokeratin and negative for CD45 and neuroendocrine markers like chromogranin and Synaptophysin. Lymphocytes were positive for CD45. A diagnosis of lymphoepithelial carcinoma was established. Screening of

EBV with anti-latent membrane protein 1 (LMP-1) antibody was negative.

The case was discussed at a multidisciplinary tumour board meeting. Keeping in view the location and extent of the tumour, its radiosensitivity, and general condition of the patient, it was decided by the board that the patient should be treated by radiotherapy alone. In view of the past experience of the patient abandoning treatment, psychological assistance to motivate him to complete his treatment was provided to the patient. The patient was started on a full course of radiotherapy and was kept on follow-up as per protocol of the radiation oncology department.

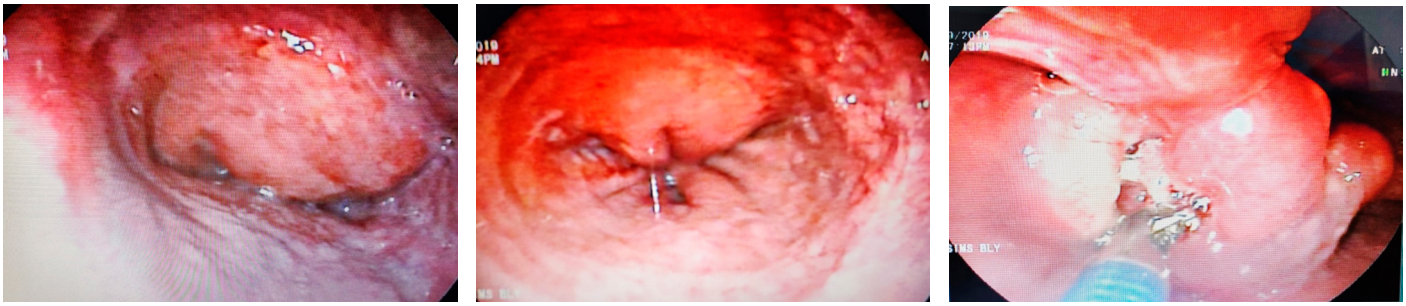

Fig. 5. (A–C) Upper GI endoscopy showing a pyriform fossa lesion.

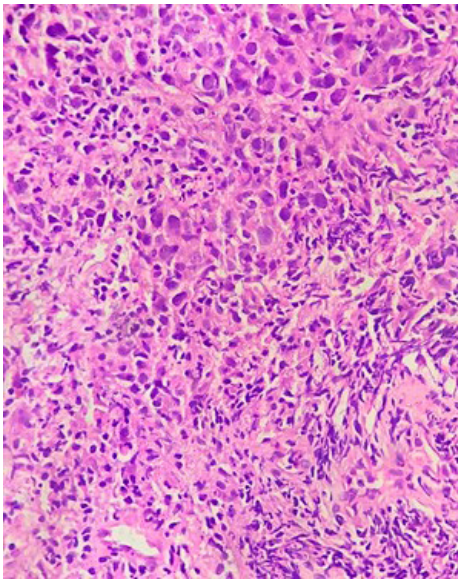

Fig. 6. Histopathological examination: H&E (40x): Large polygonal tumor cells intimately admixed with small lymphocytes.

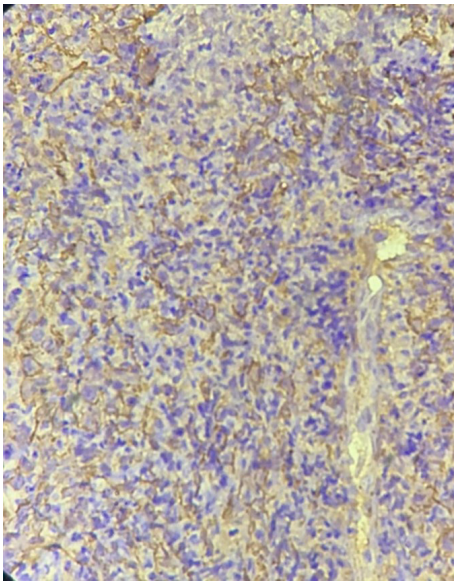

Fig. 7. Immunohistochemisty (40x): Tumor cells positive for pancytokeratin.

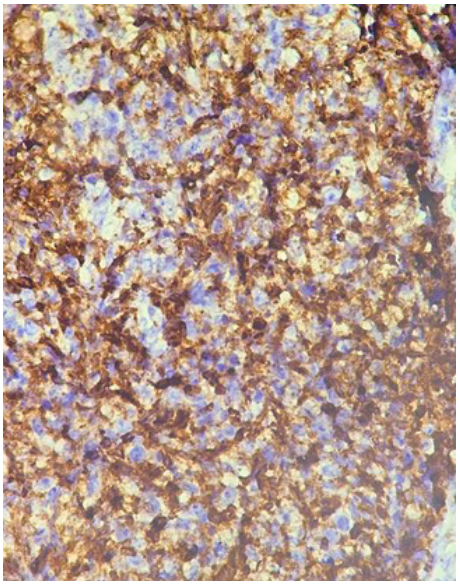

Fig. 8. Immunohistochemisty (40x): showing lymphocytes positive for CD45.

DISCUSSION

Lymphoepithelial carcinoma was first described independently yet simultaneously by Regaud and Schminke in 1921 [9]. It was reported that tumour is usually seen in patients between the age of 50 and 70 years. It is an exceedingly rare and aggressive neoplasm which has a high propensity for early cervical node metastasis and 75% of patients already have a cervical node metastasis at the time of diagnosis [10]. This was true in case of our patient. The common risk factors for the development of this condition include alcohol and tobacco use. This was not the probable cause in our patient.

The sites of the primary LEC in non-nasopharyngeal cases are tonsils, base of the tongue, salivary glands, supraglottic region, nasal cavity and hypopharynx. Diagnosis can be challenging as well as late when tumour is present in hidden submucosal sites. Hypopharynx, like in our case, is one of such sub-sites. Most commonly it is diagnosed when a metastatic neck node patient with an unknown primary focus is investigated. The patients present with complaints such as throat pain, visible mass at the primary tumour site, hoarseness of voice, dysphagia or cervical swelling depending on the site of involvement. In squamous cell carcinoma (SCC) of the larynx, hoarseness is the presenting complaint while dyspnea and stridor are more common in subglottic space carcinoma. Ear pain, pain around thyroid cartilage and airway obstruction occur in advanced cases of squamous cell carcinoma. It is very difficult to differentiate between the two based on symptomology.

In our patient, despite him being investigated twice in one year with white light direct laryngoscopy (first direct laryngoscopy and then flexible fiber-optic laryngoscope) with multiple biopsies, no definitive diagnosis could be made and doubt was raised only on visualizing with narrow-band imaging due to the submucosal nature of growth. On the other hand, in cases of squamous cell carcinoma of the larynx if a symptomatic patient reaches a surgeon for evaluation, mostly there is a visible lesion which can be diagnosed by laryngoscopy and biopsy before the disease progresses to advanced stage.

On radiological evaluation, while squamous cell carcinoma of the larynx presents with contrast-enhancing exophytic or infiltrative lesions which may erode the adjoining cartilages, SCC of subglottic areas may show endoluminal growth as well. Extensive growths may show infiltration in para-laryngeal soft tissue

Tab. I. Cases of hypopharyngeal LEC in the literature [14].

Study	Year	Total cases	Number of LECH cases	Presenting Symptoms	Findings	Treatment modality
Dockerty et al.	1968	01	01	Neck mass	Hypopharyngeal mass	Radiotherapy (RT)
Ferlito A.	1977	2052	01	Neck mass	Primary in pyriform fossa with bilateral neck nodes	RT
Stanley R.J. et al.	1985	06	01	Neck mass, Dysphagia, Hoarseness	Primary in subglottis, extending to supraglotits	RT
Manmillan et al.	1996	08	04	Hoarseness, Neck mass, Dysphagia	Primary in pyriform fossa with multiple secondaries in neck	Surgery, adj RT
Dubey et al.	1997	34	02	Dysphagia	Primary in subglottis	Surgery, adj RT
D Seitz et al.	2018	02	02	Not reported	Pyriform fossa primary with bilateral neck nodes	RT
Acuna et al.	2019	10	03	Dysphagia, Neck mass	Necrotizing lymph node, primary in pyriform fossa	Surgery, RT, Adj Chemo

structures and spaces. In contrast, LEC usually presents as submucosal growths entirely beneath the intact mucosa. Early-onset cervical lymphadenopathy is noted in the majority of cases and there are more cases of growth abutting the cartilages than invading them. We noted a similar finding in our case. Because of the rarity of this variant, there is not much description in literature.

As the tumour cells express cytokeratin, it is important to distinguish between LEC and lymphoma or melanoma. This is achieved by IHC examination with melanocyte differentiation markers (HMB45 or Melan – A) and lymphoid markers. It is also important to rule out that primary nasopharyngeal carcinomas may give metastases which may mimic the primary tumour elsewhere. Non-nasopharyngeal LEC is very less likely to be associated with Epstein-Barr virus (EBV) unlike its nasopharyngeal counterpart. In our case, the test for EBV came out to be negative. Macmillan et al. [1] concluded that LEC is not associated with EBV in patients of non-Asian descent. Marioni et al. [11] observed that the role of EBV is limited in laryngeal LEC. In their study of 34 laryngeal LEC cases, only 4 came out to be positive for EBV, out of who 10 were screened.

Treatment for LEC has always remained controversial. Surgery and radiotherapy have stayed the main treatment in the published literature. Laryngeal LEC is a radiosensitive disease and therefore radiotherapy is considered as the mainstay of treatment. Dubey et al. [9] in their study of 34 patients described three treatment strategies, namely – radiation therapy as the mainstay (as it is a highly radiosensitive tumour), excision of the primary tumour followed by radiotherapy in extensive disease and surgery alone in locally advanced cases. The surgical process includes laryngopharyngotomy, bilateral neck dissection with flap reconstruction. The overall 5-year survival rate in these patients was only 39%. Neoadjuvant chemotherapy has been recommended in very few studies to reduce the disease volume in the presence of positive lymph nodes [14].

Early attempt at molecular tissue examination may help the clinician arrive at a confirmed diagnosis. Lymphoepithelial-like – head and neck squamous cell carcinomas (HNSCC) are very often difficult to be detected on routine white light endoscopy as they do not usually involve surface epithelium and grow submucosally before becoming symptomatic. Head and neck lymph node metastasis by squamous cell carcinoma of unknown primary site which shows lymphoepithelial growth pattern needs to be investigated with panendoscopy if direct endoscopy misses the affected area.

According to Faisal et al. [14], 26% patients were treated with surgery, 57% with a combination of surgery and radiotherapy, and 17% with chemo-radiotherapy. They concluded that the outcome of surgery is good if the disease is in its early stage; for advanced cases, a combination or radiotherapy alone are the treatment of choice.

CONCLUSION

LEC is a rare entity in the larynx and more so, extremely rare in the hypopharynx. It is essential to distinguish it from squamous cell carcinoma. Immunohistochemistry is the basis of a confirmed diagnosis. As most of hypopharyngeal LECs arise from sites where it is difficult to diagnose them early, a possibility of LEC should always be kept in mind when dealing with cases presenting with dysphagia, especially with cervical lymphadenopathy. As this tumour is extremely radiosensitive, radiotherapy should be the main treatment option, especially in advanced cases. Surgery can be considered for treatment in early localized disease.

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