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A Rare Case of Locally Advanced Sinonasal Lymphoepithelial Carcinoma

Papadopoulou AM[1*], Liapi A[1] and Kostopoulou A[2]

[1]Department of Otorhinolaryngology, "G. Gennimatas" Athens General Hospital, Athens, Greece

[2]Department of Pathology, "G. Gennimatas" Athens General Hospital, Athens, Greece

[*]Corresponding author:

Anna-Maria Papadopoulou,
Department of Otorhinolaryngology, ENT Department, "G. Gennimatas", Athens General Hospital, Athens, Greece, Tel: +306977013872;
E-mail: annamariadc@hotmail.com

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1. Abstract

Sinonasal lymphoepithelial carcinoma (SLEC) is an extremely rare malignant tumor of the sinonasal tract. In this case report, we present a case with locally advanced disease of the posterior ethmoid cells. We also aim to review the clinical, radiological and pathological features, as well as the available treatment strategies, contributing to the literature of this rare malignancy.

Our patient presented with unilateral nasal congestion, discharge, recurrent epistaxis, aural fullness, diplopia and visual disturbance. Imaging revealed an extensive osteolytic lesion of the right nasal cavity with intraorbital and intracranial invasion. Histopathological examination of posterior ethmoid cell mucosa demonstrated undifferentiated malignant cells, associated with lymphoplasmacytic infiltration, while the immunohistochemistry was positive for pancytokeratin. A final diagnosis of EBV-positive SLEC was rendered and the patient was treated with concomitant chemo-radiotherapy. To our knowledge, this is the first case report of SLEC arising from the posterior ethmoid cells with invasion into the orbit and middle cranial fossa.

2. Introduction

Sinonasal lymphoepithelial carcinoma (SLEC) is an extremely rare malignant tumor of the sinonasal tract. It has been defined by the World Health Organization (WHO) as ''a poorly differentiated squamous cell carcinoma or histologically undifferentiated carcinoma accompanied by a prominent reactive component of small, mature lymphocytes and plasma cells, morphologically similar to the undifferentiated subtype of nasopharyngeal carcinoma'' [1]. It is highly associated with positive Epstein-Barr virus (EBV) staining, in opposition to undifferentiated nasopharyngeal carcinoma [2]. Moreover, these two neoplasms are separated by their location and clinical course and are recently considered as different disease entities [3]. Although salivary gland LEC has been better studied, sinonasal occurrence is rare, with approximately 40 cases documented in the literature [4]. The lack of intimate association between the surface epithelium and lymphoid tissue in the nasal cavity and paranasal sinuses could be a possible explanation [5]. The majority of cases were reported in EBV-endemic regions, such as Southeastern Asia [2]. Most patients present with locally aggressive disease, but tend to respond well to radiotherapy in combination to surgery and/or chemotherapy [4].

In this case report, we present a patient with locally advanced disease of the posterior ethmoid cells. We also aim to review the clinical, radiological and pathological features, as well as the available treatment strategies, contributing to the literature of this rare malignancy.

3. Results

A 74-year-old Caucasian man with a history of smoking presented to the otorhinlolaryngology department with symptoms of unilateral nasal congestion, discharge, episodes of recurrent epistaxis from the right nasal cavity and right aural fullness for the previous 3 months. During the last 2 weeks he complained of facial pain and pressure, as well as diplopia and visual disturbance on the same

side. The nasendoscopy examination revealed bulging of the right nasopharyngeal wall, which blocked the opening of the Eustachian tube. Interestingly, the nasopharyngeal mucosa appeared to be normal. Right ear examination showed otitis media with effusion. Regional neck lymphadenopathy was not palpated. A paranasal sinus CT scan showed opacification of the right ethmoid cells and maxillary sinus by an extensive soft tissue, osteolytic lesion, which expanded beyond the floor of the right orbit and into the middle cranial fossa, infiltrating the pituitary gland and eroding the sphenoid bone, the clinoid processes, the sella and the carotid foramen (Figure 1 and 2). Subsequently, the patient underwent endoscopic sinus surgery under general anesthesia, where middle antrostomy and anterior-posterior ethmoidectomy were performed. We obtained biopsies from suspicious mucosa of the posterior ethmoid cells and nasopharyngeal mucosa. Histopathological examination demonstrated irregular sheets and nests of undifferentiated malignant cells, associated with lymphoplasmacytic infiltration. The tumor cells were stained positive for CKAE1/AE3, p63, CK5/6, p40, CK8, CK14(focally) and negative for p16 and synaptophysin, according to the immunohistochemical analysis that followed. In situ hybridization assay for the Epstein-Barr virus-encoded RNAs (EBER) was also positive. Biopsies from the nasopharyngeal mucosa were negative for malignancy. A final diagnosis of SLEC was rendered, based on the clinical and histopathological findings. A PET-CT scan did not reveal any distant metastasis and the tumor was staged as T4N0M0. Our tumor board decided to offer the patient treatment with radiotherapy and chemotherapy due to local spread into the orbit and cranial cavity.

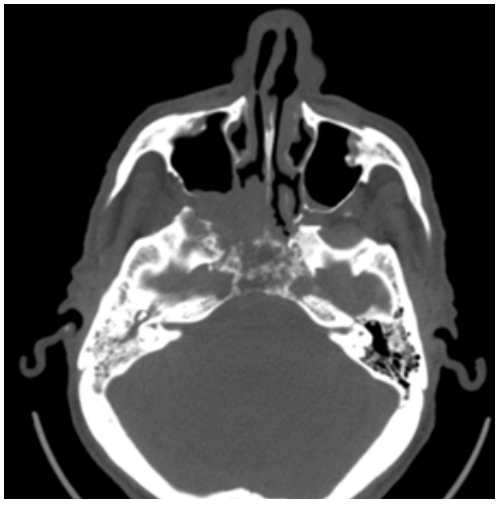

Figure 1: CT scan. Opacification of the right maxillary sinus by an osteolytic lesion, invasion of the middle cranial fossa.

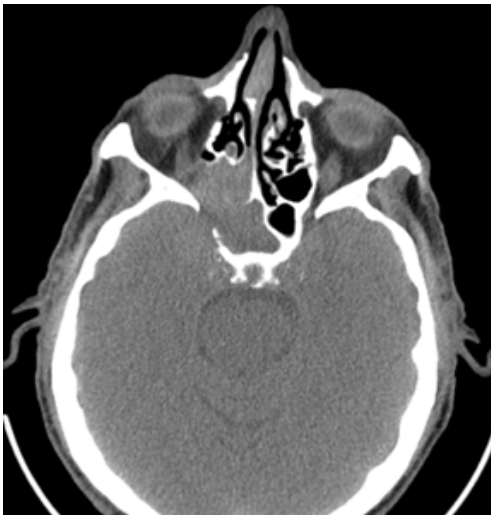

Figure 2: CT scan. Opacification of the right ethmoid cells, intraorbital invasion.

4. Discussion

Schminke and Regaud originally described LEC back in 1921 [6,7]. In the head and neck region, it usually develops in the nasopharynx, salivary glands, and larynx. Sinonasal occurrence is extremely rare, with approximately 40 reported cases, according to our literature search. Notably, only one case of ethmoid cell involvement has been documented [5]. Men in their fifth to seventh decades of life are more frequently diagnosed with SLEC [8]. This neoplasm has been associated with genetic susceptibility, exposure to chemical carcinogens, as well as latent EBV infection [3]. The largest case series of SLEC in the literature were conducted in EBV endemic areas [2]. It has been suggested that the high incidence of LEC in such areas, such as Southeast Asia, may be associated with EBV infection [3]. The exact role of EBV in the tumorigenesis is still not known [5] and its presence does not seem to offer prognostic importance concerning diagnosis, survival or response to treatment [9]. EBV status could only be useful in determining distant tumors as metastases [10]. Smoking, tobacco chewing, HPV infection and ethanol do not appear to be risk factors [11].

Early stage disease is usually asymptomatic and can be discovered incidentally [12]. Most patients suffer from non-specific sinonasal symptoms, such as obstruction, epistaxis and facial pain [13]. In cases of invasive growth, proptosis and cranial nerve palsies can be caused [4]. One patient presented with anosmia and ageusia due to invasion to the olfactory bulb and frontal lobe [5], while in another case, the tumor mimicked juvenile angiofibroma because of hyper-vascularity [14]. According to previous reports, SLEC has the tendency to spread locally, without neck metastases, except for one case [10]. Our patient also presented with locally advanced disease without cervical or retropharyngeal lymph nodes. Distant spread recurrence has been described. Interestingly, distant metastases do not contain reactive lymphocytes, which confirms the malignant nature of only the epithelial component of the tumor [5].

There are no specific clinical or radiological features to differentiate SLEC from other locally destructive tumors, such as squamous cell carcinomas or lymphomas [13]. The definite diagnosis of a SLEC can only be established by histology and immunohistochemical analysis.

Tumours are composed of syncytial clusters of crowded, large, undifferentiated cells arranged in lobules, nests, trabeculae or cords, and in an intimate relationship with a lymphoplasmacytic infiltrate. The malignant cells typically have large round nuclei, vesicular chromatin, prominent nucleoli, and ill-defined cell borders (a syncytial pattern); occasional tumour cell spindling may be encountered. Necrosis or keratinization is typically absent. In some cases, thick fibrous septa separating tumour islands may be observed. Extracellular amyloid deposits may be present [11,13]. Immunohistochemical staining is positive for pancytokeratin marker (MNF 116) and MIB-1 [13]. SLEC histology and immunohistochemical analysis are similar to nasopharyngeal undifferentiated carcinoma [15]. Although the lymphoid infiltration in SLEC is reported to be less prominent, their differentiation relies mostly on tumor location [4,15]. In our case, for example, the origin of the tumor appeared to be from the ethmoid cells, while the nasopharyngeal mucosa seemed normal and nasopharyngeal biopsies were negative for malignancy. These data lead to the final diagnosis of SLEC. Another malignant and highly aggressive neoplasm, which must be distinguished from SLEC, is sinonasal undifferentiated carcinoma (SNUC). SNUC is characterized by increased mitotic activity and apoptosis, while certain types of cytokeratins are expressed. Moreover, it is not positive for EBV [5,10]. In addition, melanocytic and mesenchymal markers can differentiate SLEC from non-epithelial tumors such as melanomas and sarcomas [16]. Finally, extranodal natural killer/T-cell lymphoma (ENKTL) is often histologically undifferentiated and associated with EBV, mimicking SLEC. Nevertheless, it is cytokeratin negative and characteristically positive for CD3 and CD56 [8,11]. When lymphomas are suspected, flow cytometry of separate specimen can be insightful [4].

Because of the limited reported cases of SLEC in the literature, no treatment guidelines have been established. Traditionally, surgery has been the initial treatment of choice, regarding epithelial tumors in the nasal cavity and paranasal sinuses [13] and can be considered in cases of limited disease [14]. It is interesting though, that SLEC demonstrates high sensitivity and excellent initial response to radiotherapy [17]. More advanced techniques such as intensity modulated radiation therapy are associated with less complications related to radiation toxicity and better local control [15]. Some authors have also suggested additional chemotherapy in cases of locally advanced or metastatic disease [18, 19]. In light of brain and orbital invasion, our tumor board decided to offer our patient concomitant chemo-radiotherapy.

The prognosis of SLEC depends on the stage [17, 20] and in comparison with other poorly differentiated sinonasal epithelial tumors, it remains favorable, despite of the fairly common local spread at the time of the diagnosis [21]. The 5-year survival rate is estimated to be approximately 78% [4]. Tumor biological characteristics such as radiosensitivity could be responsible for this. Another theory suggests that the prominent lymphoid tissue represents a host response against the tumor [10]. Nevertheless, the limited available clinical reports do not include prolonged follow-up periods and as a result late relapses or metastases have not been frequently studied and reported.

5. Conclusion

In conclusion, SLEC is an extremely rare neoplasm, which should be differentiated from other malignancies. We present a case of EBV-positive SLEC of the posterior ethmoid cells and provide all relevant clinical, radiological and histopathological information, contributing to the limited available literature. We also suggest chemoradiotherapy for locally advanced tumors and regular follow-up with CT scans. To our knowledge, this is the first case report of SLEC arising from the posterior ethmoid cells with invasion into the orbit and middle cranial fossa.

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