Primary Lymphoepithelial-Like Carcinoma of the Parotid Gland- Case Presentation

Background/Aim: Primary Lymphoepithelial carcinoma (PLEC) is a rare subtype of salivary gland cancers, which comprises only 0.4% of salivary malignant neoplasms and only a few cases have been presented previously. Case report: A patient with PLEC of the parotid gland, its management and the available literature are presented. A 53-year-old woman with initial lesion of a lump in the region of the right parotid received treatment with antibiotics which did not lead to improvement. MRI was performed that recorded the presence of a tumor in the right parotid gland and the patient subsequently underwent excision biopsy. The histopathological evaluation together with additional immunohistochemical positive staining of EMA+, EGFR+, p63+, CK 5/6+, AE1/AE3+ established the diagnosis of PLEC. A PET-CT scanning has shown nor primary mucosal source neither skin lesion to account for any possible metastatic disease, consequently a course of adjuvant post-operative radiotherapy to the region of the right parotid gland was performed. Conclusions: In the differential diagnosis of a parotid gland lump should be included the possibility of a rare salivary gland neoplasm such as PLEC. Surgical excision and radiotherapy have been proposed for the treatment of early and advanced neoplasm stages. Ages of the patient, stage of the neoplasm as well as type of therapy are significant and individual variables for the prediction of the prognosis. Key words: Lymphoepithelial Carcinoma, Salivary Gland Neoplasms, Parotid Neoplasms, Histopathology, Immunohistochemistry, Prognosis, Treatment.

Introduction

Primary Lymphoepithelial carcinoma (PLEC) is a very unusual subtype of salivary gland cancers, which involves mainly the parotid gland1,2. Furthermore for the salivary PLEC have been used different terms as: undifferentiated carcinoma with lymphoid stroma, malignant lymphoepithelial lesion, lymphoepithelioma-like carcinoma, undifferentiated carcinoma and carcinoma ex lymphoepithelial lesion1. PLEC is analogous and exhibits identical histopathological characteristics as non-keratinizing, undifferentiated nasopharyngeal carcinomas (NPC)3. However PLEC arises in organs other than nasopharynx, such as larynx1, tonsils1, lung6, thymus1, stomach and duodenum8, breast9, renal pelvis and urinary bladder10, uterine cervix11, endometrium12, ovary13, vulva and vagina14. The experience in PLEC is restricted to a small number of case reports and series, most of which describe female patients in specific geographic regions such as Arctic Circle, Greenland and Southern China, with documented association of Epstein-Barr virus (EBV) implication. Consequently the above mentioned case series proposed a racial, gender, and geographic predilection to the disease2,15-23. The scientific evidence presenting cases of PLEC in other regions are restricted with significant geographic variations15,16,23-25.

Case report

A 53-year-old Caucasian woman was referred to our department for the management of recently enlarging
Afterwards the lower right wisdom teeth were extracted and the patient received treatment with a different antibiotic (clindamycin) that diminished the submandibular lesion whereas led to no improvement in the parotid lump. The neurological evaluation of the patient confirmed that bilateral facial nerve function was unimpaired in any way. Again her medical history was reviewed in detail and confirmed that the patient had no history of skin cancer or other type of malignancy in the head and neck region. An MRI was performed and there was recorded the presence of a malignant growth in the right parotid gland. A scintigraphy (i.v. Tc99m) in the salivary gland recorded two lumps in the lower part of right parotid gland that took on no Tc99m, so they were not parts of the parenchyma of the gland (Figure 2). Afterwards a Fine Needle Aspiration (FNA) for diagnostic cytology was conducted, which confirmed the malignant nature of the lesions.

Figure 1. Clinical appearance of Primary Lymphoepithelial carcinoma (PLEC) located in the region of the right parotid

Figure 2. MRI and scintigraphy (i.v. Tc99m) imaging of PLEC

Figure 3. A Infiltrative neoplasm adjacent to normal parotid gland parenchyma that includes aggregates of lighter staining neoplastic foci in a background of darker staining lymphocytic cell infiltrate (H/E, X 40 magnification)

Figure 3. B Cohesive aggregates or clusters of neoplastic cells with enlarged vesicular nuclei and prominent nucleoli, characterized by a syncytial growth pattern (H/E X 100 magnification)
Total parotidectomy with nerve preservation and unilateral upper neck dissection was performed, and the histopathological evaluation with H&E routine staining of the specimens (Figure 3), together with additional immunohistochemical positive staining of EMA+, EGFR+, p63+, CK 5/6+, AE1/AE3+ (Figure 4), and negative of LCA-, CA15-3-, TTF1-, S100-, CD34-, SMA-, CK7-, CK20- established the final diagnosis of PLEC.

A PET-CT scanning has shown nor primary mucosal source neither skin lesion to account for any possible metastatic disease, consequently the patient received a course of adjuvant post-operative irradiation to the right parotid bed and the right neck including levels 1b, 2, 3, 4 and 5. She has received a post-operative dose of 60Gy in 30 sessions to each of these areas. No concomitant chemotherapy was used. Six years later, there was no metastasis neither in the head and neck nor in the lymph nodes. Excessive bone loss and highly increased DMFT were observed in the area which the radiotherapy was previously performed.

**Discussion**

Primary Lymphoepithelial carcinoma (PLEC) of the major salivary glands is extremely uncommon neoplasm which constitutes 0.4% of the total salivary gland malignancies in non-endemic regions. Medical/dental personnel has available inadequate scientific information limited to disperse case series derived from endemic regions in order to decide alternative ways of treatment and to advise patients with PLEC26.

Previous literature recorded elevated frequencies of PLEC in specific geographic regions such as in Arctic Cycle (Greenland, Canada, Alaska), Southeastern China, and Japan1. In these areas PLEC usually involves the parotid gland with female predilection and exhibits a higher invasive course27. In a recent study with two hundred and thirty-eight cases of PLEC with most of the patients of Caucasian origin (81.2%), the median age at diagnosis was 62 years with higher prevalence in ages 50–70, without gender preference28.

The clinical features of salivary PLEC are consistent of a salivary gland mass/swelling, usually located in parotid gland. The onset of the lesion has been described as of considerable diversity, which in a percentage of the cases may appeared from 7 days to 20 years before observing their initial symptoms29,30. In some cases patients is possible to encounter an accelerated...
augmentation in neoplasm size, however the reported data presented an extensive variation (15.9–75%)\textsuperscript{29,30}. Furthermore it has been reported that infrequent symptoms are pain or tenderness (10.1–25%)\textsuperscript{29,30}, and facial pareshesia (1.4–20%)\textsuperscript{27,28,30}. The diagnostic procedure of PLEC includes mainly radiological techniques (CT, MRI), and fine-needle aspiration biopsy. A previous study evaluated the diagnostic efficiency of fine-needle aspiration cytology method which proved to be sensitive in 78.6% of 14 PLEC cases\textsuperscript{31}. CT and MRI radiological techniques have been considered as useful supplementary investigations for the diagnosis, preoperative assessments and biopsy guidance in PLEC cases, although these tumors in a study for their imaging characteristics on CT and MRI revealed nonspecific attenuation and signaling\textsuperscript{32}. In addition is required to rule out a possible regional metastasis from the nasopharynx, because this event may demand a completely distinct therapeutic approach. Furthermore due to histological similarity of non-keratinizing, undifferentiated nasopharyngeal carcinoma (NPC) to salivary PLEC, it has been recommended in such cases, endoscopy and random biopsy of smooth-appearing nasopharyngeal mucosa in order to confirm the diagnosis\textsuperscript{30}.

The diagnosis of PLEC is based predominantly on histological characteristics, which display well-circumscribed nodules, including anaplastic cells with prominent cosinophilic nuclei located in nests, sheets, and cords of syncytial-like growth pattern, and surrounded by moderate to heavy lymphocyte infiltrates\textsuperscript{33}. Additional immunohistochemical evaluation may be required, with positive staining of neoplastic cells for cytokeratin, epithelial membrane antigen, and variable expression of EBV and of lymphoid cells for cytokertatin, B-cell markers suggestive of B-cell and T-cell presence, in order to confirm the initial histological diagnosis\textsuperscript{34}.

In most PLEC tumors of salivary glands was reported the increased infiltration of CD20+B lymphocytes and CD3+T lymphocytes in the tumor cell nests and the surrounding stroma and germinal centers. The above mentioned infiltration perhaps provoked a strong host immune response, which is possible to guide PLEC to an approximately better prognosis\textsuperscript{33}.

Differential diagnosis of PLEC in histological level includes squamous and mucoepidermoid carcinoma with abundant lymphocytic infiltration, poorly differentiated large cell carcinoma of salivary origin and nasopharyngeal carcinoma with parotid extension\textsuperscript{15}. The nasopharyngeal carcinoma as mentioned previously may required a challenging differential diagnosis to distinguished and is possible to demand a detailed clinical, imaging, histological and immunohistochemical investigation\textsuperscript{1}.

Salivary PLEC regularly metastasizes to the regional lymph nodes (45.1%), usually with extensive lymph node involvement (69.1% N2 out of all lymph nodes positive infiltration) whereas in the same recent non-endemic region study, the incidence of distant metastasis in salivary PLEC, has been reported less than 10%, and the authors stated that routine radiological investigations in remote areas of the body are not always justified\textsuperscript{29}. In the above mentioned study was also revealed that in comparison to the parotid glands, submandibular gland PLECs displayed an increased percentage of occurrences in the American Indian, Aleutian, Eskimo, Asian population, presented with T3-T4 disease and regional metastasis. The previous observation was not significantly modified the survival rate in total of PLEC cases in parotid and submandibular gland sites\textsuperscript{28}.

The origin and pathogenesis of PLEC has been proposed to related with malignant transformation of a myoepithelial island or alternatively with malignant transformation of glandular and ductal insertions in intraparotid lymph node\textsuperscript{15}. The implication with EBV, since EBV was isolated in >90% of endemic PLEC patients, has proposed a possible function for the virus in the etiopathogenesis of PLEC but the association remains in dispute, taking consideration that EBV usually was undetected in the non-endemic PLEC cases\textsuperscript{27}. Additional research papers investigating PLEC neoplasms, reported viral presence in clonal episomal form and viral LMP-1 oncoprotein expression, supporting EBV role in PLEC tumorigenesis\textsuperscript{35, 36}. Moreover in support of PLEC and EBV association, it has been suggested that EBV is possible to play a role in younger patients in Asian populations, because it was previously reported that primary infection of EBV in children of families with lower socioeconomic status was an early event\textsuperscript{57}. Furthermore it is well documented that primary EBV infection usually involves children of younger ages, causing approximately 90% seropositivity in early adulthood. Subsequently EBV persists in the host for life associated with low grade infections in the oropharynx, salivary ductal cells, and dormant in B-lymphocytes. Nevertheless the findings of a study from a non-endemic region created the probability of a separate disease mechanism and etiopathogenesis in a Caucasian predominant population\textsuperscript{28}. Taking consideration that adult populations worldwide are seropositive for EBV\textsuperscript{38} it is possible that alternative viral immune control functions operate in distinctive geographic regions and ethnicities. The above mentioned aspects contribute to a supplementary level of complication in PLEC etiopathogenesis, part of which is associated mainly with EBV in specific geographic regions\textsuperscript{28}. Furthermore considering the histopathological similarity between nasopharyngeal carcinoma and PLEC and their interrelation with EBV, it has been proposed a hypothesis of a potential correlation between the two, which may influenced by common risk factors such as diets containing high quantities of nitrites\textsuperscript{28}. 


A previous clinicopathologic study, investigating the immunohistochemical characteristics of PLEC pointed out that lower level, or complete loss of expression, of p53, c-erb B-2 oncoproteins, and low rate of EGFR mutation were significantly correlated to a more favorable prognosis in PLECs of salivary glands. Furthermore in the same research paper was detected positive bcl-2 immunostaining with moderate to strong intensity in the majority of the cases (20 in 21). This finding suggested that increased expression of bcl-2 protein created a specific growth enhancement to the EBV-infected B cells, and proposed simultaneously that the bcl-2 over-expression it is possible to be associated with a favorable prognosis.

The treatment for the salivary gland tumors remains challenging for most of the cases, especially for salivary PLEC, surgical excision with postsurgical radiotherapy together with neck dissection in case of cervical metastasis, were considered as the treatment of choice. In a recent study with most of the cases of Caucasian origin, the occurrence of cervical metastasis did not significantly affected the survival expectancy, in addition it has been reported a total survival difference, especially in early disease, in patients who performed both surgical interventions and radiotherapy. Whereas in a select cohort of 22 patients with Stage III PLEC who performed neck dissection, a significantly better survival was recorded. In the above mentioned study was also reported that in cases which performed postsurgical radiotherapy, was recorded an increased period of time free of recurrence, however no significant difference was observed in overall survival. Five year and ten year survival is 77% and 56% respectively whereas older age and advanced stage are supplementary significant and individual factors of worst survival.

Conclusions

In conclusion in the differential diagnosis of a parotid gland lump should be included the possibility of a rare salivary gland neoplasm such as PLEC. Consequently, the medical/dental personnel must be informed for the diagnostic sequence, the management and the available literature of such lesion. Surgical excision and radiotherapy have been proposed for the treatment of early and advanced neoplasm stages. Ages of the patient, stage of the neoplasm as well as type of therapy are significant and individual variables for the prediction of the prognosis.

References


