Lymphoepithelial carcinoma of the salivary glands: case report of a rare cancer and review of the literature

Holz-Sapra, E; Glanzmann, C; Schmid, S; Went, P; Studer, G

Abstract: Objective: Lymphoepithelial carcinoma (LEC) of the salivary glands is a very rare condition especially in the Caucasian population. We herewith contribute a case of a Caucasian woman with LEC of the parotid gland. Furthermore we present a literature review on LEC of the major salivary glands (MSG) of the past 32 years. Materials and Methods: We reported an own case and performed a review of the medical literature (1980-2012). Results: Case report: After a Follow-up (FU) of 5 years after treatment with postoperative IMRT and concomitant carboplatin, our patient has no signs of relapse. Review: We found 404 cases with LEC of the MSG published in 33 articles over the last 32 years. The mean age of the patients was 49 years (16-86); 56% were female. 95% of the cases have been treated and published in Asia (China, Taiwan). Only 17 of the 404 cases (4%) reported in 15 publications, Caucasian patients were affected. Information on treatment and outcome was not available in 75% and 72%, respectively. After a mean FU of 5.5 years (range 0.5-14) 66 of 84 (79%) patients with reported FU showed no evidence of disease. Conclusion: LEC of the salivary glands is a rare disease especially in Caucasian populations with only 4% of published LEC cases in the reviewed literature. In only 21% of the reports, clinical information on treatment and outcome was provided. Based on the limited information available from published reports, the value of radiotherapy remains unclear.
Lymphoepithelial Carcinoma of the Salivary Glands: Case Report of a Rare Cancer and Review of the Literature

Edna Holz-Sapra¹, Christoph Glanzmann², Stefan Schmid³, Philip Went⁴, Gabriela Studer⁵

¹, ², ⁵Department of Radiation Oncology, University Hospital Zurich, Raemistr. 100, 8091 Zürich, Switzerland
³Klinik Bethanien, Praxis für ORL und Gesichtschirurgie, Toblerstr. 51, 8044 Zürich, Switzerland
⁴Pathologie Institut Enge, Tödistrasse 48, 8027 Zürich
Gabriela.Studer@usz.ch

Abstract
Objective: Lymphoepithelial carcinoma (LEC) of the salivary glands is a very rare condition especially in the Caucasian population. We herewith contribute a case of a Caucasian woman with LEC of the parotid gland. Furthermore we present a literature review on LEC of the major salivary glands (MSG) of the past 32 years.

Materials and Methods: We reported an own case and performed a review of the medical literature (1980-2012).

Results: Case report: After a Follow-up (FU) of 5 years after treatment with postoperative IMRT and concomitant carboplatin, our patient has no signs of relapse.

Review: We found 404 cases with LEC of the MSG published in 33 articles over the last 32 years. The mean age of the patients was 49 years (16-86); 56% were female. 95% of the cases have been treated and published in Asia (China, Taiwan). Only 17 of the 404 cases (4%) reported in 15 publications, Caucasian patients were affected. Information on treatment and outcome was not available in 75% and 72%, respectively. After a mean FU of 5.5 years (range 0.5-14) 66 of 84 (79%) patients with reported FU showed no evidence of disease.

Conclusion: LEC of the salivary glands is a rare disease especially in Caucasian populations with only 4% of published LEC cases in the reviewed literature. In only 21% of the reports, clinical information on treatment and outcome was provided. Based on the limited information available from published reports, the value of radiotherapy remains unclear.

Keywords- Lymphoepithelial Carcinoma, salivary Gland, Caucasian, Radiotherapy LEC, Outcome LEC

I INTRODUCTION

Lymphoepithelial carcinoma (LEC) of the salivary glands is a very rare finding especially in Europe. It accounts for approximately 0.4% of malignant salivary gland tumors [1].

Salivary glands tumors are in general uncommon accounting for less than 3% of all head and neck tumors. About 25% of all tumors of the parotid glands are malignant [2]. In the world, the annual incidence of malignant tumors of the parotid gland vary between slightly less than 2 and greater than 0.05 per 100000 [3]. The most common malignant salivary glands tumors include mucoepidermoid carcinoma and adenoid cystic carcinoma, which together comprise approximately one-half of all malignant salivary gland tumors [2].

LEC of the parotid glands has a strong racial prevalence being more common in Eskimos and among southeastern Chinese. Eskimo and Asian population have the greatest incidence of LEC [4]. The incidence of malignant tumors of the salivary glands in Greenland is described in a report of Cleary et al with 3.9% in males and 7.7% in females [5]. Over 90% of these tumors occur in the parotid gland, and > 90% are LEC.

In 1921 A. Schmincke [6] as well as Regaud and Reverench [7] independent from each other described the first time a nasopharyngeal neoplasm characterized by undifferentiated epithelial tumor cells surrounded by lymphoid stroma. In 1962 Hildermann introduced the term “Lymphoepithelial Carcinoma” (LEC) [8]. Subsequently, morphologically similar tumors were described at various primary sites such as lacrimal and salivary glands, tonsil, thymus, lung, breast, uterus, stomach, urinary bladder, breast, pancreas, renal pelvis, ureter, mandible, vagina, rectum, trachea, kidney and skin. LEC is a specific subtype of undifferentiated carcinoma [9] and shares histological features with nasopharyngeal carcinoma and benign lymphoepithelial lesion [10]. In the literature the LEC outside the nasopharynx is also called Lympho-epithelioma-like carcinoma. The World Health Organization (WHO) defines it as undifferentiated carcinoma with lymphoid stroma [11].
In general, LEC may or may not be associated with Epstein-Barr virus (EBV) [12, 13]. There has been described a case of a LEC arising from a gland in which a benign lymphoepithelial lesion had been diagnosed before [14]. This might implicate a malignant transformation, but most LECs are not diagnosed on the background of a benign lymphoepithelial lesion and probably develop de novo [1]. LEC associated with EBV infection has been described in endemic areas such as Southeast Asia [12].

We report a case of LEC of the parotid gland to contribute to the limited case reports of this very rare tumor occurring to Caucasians. Furthermore, we performed a systematic review of the English literature of LECs of the MSGs from the last 32 years.

II MATERIALS AND METHODS

We reported one case of LEC diagnosed in the left parotid gland. Furthermore, we performed a systematic review of the English literature using MEDLINE (January 1980 – March 2013) and searched cross links manually. We included case series as well as case reports of LEC of the major salivary glands. Non-English publications and publications in abstract form only were excluded. Furthermore we excluded case series of LEC of head and neck if no details were provided for LEC of MSG. TN stage, age, gender, performed treatment and outcome have been assessed.

III STATISTICS

The Excel program was used as data basis and for statistical calculations, including mean, median and data range values. P values <0.05 were considered statistically significant, however, for this descriptive analysis no statistical calculations were required.

IV CASE PRESENTATION

A 28-year old woman presented with a swollen lymphatic node of the left side level II of the neck. Her medical history was not contributory. A fine needle aspiration cytology was carried out and showed the histopathological diagnosis of a LEC. The patient underwent a left complete parotidectomy and left modified neck dissection level II-IV, and a reconstruction of the ramus colli N. facialis with N. auricularis – transplant performed by an ENT surgeon (SS). The diagnosis of a LEC from the fine needle aspiration was confirmed by a second pathologist (Figs. 1 & 2). The lesion showed a diameter of 12 mm. The evidence of EBV was positive. In 13 of 49 lymphatic nodes cancer cells were detected. Most of lymph node metastases were located caudally of the parotid gland in level II. The maximum size of the clinically evident lymphatic node located in level II was 1.9 cm. There was no sign of extracapsular extension (ECE). The resection margin was locally less than 1 mm.

![Fig. 1 Lymphoepithelial carcinoma tissue adjacent the glandula parotis. The overview depicts a dense lymphocytic tissue, which could obscure the tumor infiltration as seen in the lower left side of the figure. Germinal centers are frequently seen. No inflammatory infiltrates are seen in the normal parotid gland (HE Staining, x5)](image-url)
Fig. 2 Detailed morphology of the tumor. Syncytial infiltrating tumor cells are large and vesicular with prominent nucleoli. Small intratumoral lymphocytes and larger centroblasts are both significantly smaller if compared to the tumor cells (HE staining, x40)

The patient was referred to our clinic for post-operative radiation therapy. The planning target volume (PTV) to be covered was extensively discussed because of some uncertainty whether the lesion in the parotid gland representing a primary of the parotid gland or an intraparotideal lymph node metastases of an undetected nasopharyngeal primary (NPC). Regarding the fact that metastases of a NPC in the parotid gland is rather unusual [15], and that endoscopic as well as radiological evaluation (MRI and PET-CT) did not show any abnormal findings in the nasopharynx the lesion was considered as a primary of the parotid gland, TN stage pT3 pN2b (13/49) M0. A biopsy of the nasopharynx was not performed. A fine needle aspiration of a slightly enlarged lymphatic node of the contralateral side showed no tumor. The patient was treated with 4 dose levels (70, 66, 60 and 54 Gy) with stereotactic integrated boost (SIB) IMRT: 66 Gy in 2 Gy to the affected lymph nodes level II and III left side (Fig. 3), 54 Gy to elective lymph nodes level IV and V. A small boost of 70 Gy in 2.11 Gy per session (PTV: 7.4 cm³) was applied to a suspect macroscopic finding (Fig. 4) in the former tumor region. A margin of 1 cm (> .5cm – 2cm, depending on anatomical structures involved) around the GTV is used as PTV considering anatomic borders like bony structures.

Fig. 3 Overview of 4 dose levels (70, 66, 60 and 54 Gy) with stereotactic integrated boost (SIB) IMRT
A concomitant chemotherapy of carboplatin (4 cycles of 90 mg each) was administered. Cisplatin was stopped after one application of 40mg/m2/week because of tinnitus.

After radiochemotherapy, chemotherapy was administered according to the scheme of Al Sarraf [16] but using carboplatin instead of cisplatin considering the risk of a recurrent tinnitus. (3 cycles carboplatin AUC 6, absolute 750 mg day 1 und 5-FU 1000 mg/m² per day, absolute 7200 mg iv. day 1-5).

The chemoradiotherapy was tolerated very well by the patient besides the expected dysgeusia, odynophagia (RTOG grade II) and mucositis (RTOG grade II). During the adjuvant chemotherapy besides a moderate nausea, a thrombopenia (RTOG grade III) and leukopenia occurred (RTOG grade II).

The patient remained under regular FU including physical examinations and diagnostic imaging. The latest MRI (43 months after end of treatment) of the head and neck was bland. Meanwhile 5 years after the completion of treatment, the patient is alive with no evidence of disease (ANED) and no late toxicity.

V RESULTS OF THE LITERATURE REVIEW ON LEC OF MSG

33 publications met our criteria [9, 17-43].

Overall we found 404 cases of LEC (excluding our own case) in the salivary glands which have been published over the past 32 years: in 323/404 cases (80%), the primary was diagnosed in the parotid gland in 54 cases (13%) in the submandibular and in 27 cases (7%) in minor salivary glands. In only 18/405 cases (5%), own case included, Caucasians were affected, please see Tables 1 and 2.
# TABLE I. SUMMARY OF ALL PATIENTS AND TUMORS CHARACTERISTICS.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>N</th>
<th>Sex</th>
<th>Age</th>
<th>Tumor Site</th>
<th>TNM Status</th>
<th>TN</th>
<th>Classification</th>
<th>Tumor Characteristics</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowland et al.</td>
<td>1992</td>
<td>1</td>
<td>M</td>
<td>60</td>
<td>PG</td>
<td>T3N1M1</td>
<td>R0</td>
<td>SCC</td>
<td>Parotid</td>
<td>RT, S</td>
</tr>
<tr>
<td>Ng et al.</td>
<td>1993</td>
<td>2</td>
<td>F</td>
<td>40</td>
<td>PD</td>
<td>T4N2M2</td>
<td>R2</td>
<td>SCC</td>
<td>Submandibular</td>
<td>RT</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>1994</td>
<td>1</td>
<td>M</td>
<td>50</td>
<td>PD</td>
<td>T1N1M0</td>
<td>R0</td>
<td>SCC</td>
<td>Parotid</td>
<td>RT</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>1995</td>
<td>2</td>
<td>F</td>
<td>60</td>
<td>PD</td>
<td>T2N2M1</td>
<td>R1</td>
<td>SCC</td>
<td>Submandibular</td>
<td>RT, S</td>
</tr>
<tr>
<td>Na et al.</td>
<td>1996</td>
<td>1</td>
<td>M</td>
<td>70</td>
<td>PD</td>
<td>T3N2M1</td>
<td>R0</td>
<td>SCC</td>
<td>Minor salivary</td>
<td>RT, S</td>
</tr>
<tr>
<td>Yoon et al.</td>
<td>1997</td>
<td>1</td>
<td>M</td>
<td>50</td>
<td>PD</td>
<td>T2N2M1</td>
<td>R0</td>
<td>SCC</td>
<td>Parotid</td>
<td>RT, S</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>1998</td>
<td>2</td>
<td>F</td>
<td>40</td>
<td>PD</td>
<td>T3N2M1</td>
<td>R0</td>
<td>SCC</td>
<td>Submandibular</td>
<td>RT, S</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>1999</td>
<td>1</td>
<td>M</td>
<td>60</td>
<td>PD</td>
<td>T4N3M1</td>
<td>R2</td>
<td>SCC</td>
<td>Minor salivary</td>
<td>RT, S</td>
</tr>
<tr>
<td>Na et al.</td>
<td>2000</td>
<td>2</td>
<td>F</td>
<td>50</td>
<td>PD</td>
<td>T2N3M1</td>
<td>R0</td>
<td>SCC</td>
<td>Parotid</td>
<td>RT, S</td>
</tr>
<tr>
<td>Yoon et al.</td>
<td>2001</td>
<td>1</td>
<td>M</td>
<td>70</td>
<td>PD</td>
<td>T3N3M1</td>
<td>R0</td>
<td>SCC</td>
<td>Submandibular</td>
<td>RT, S</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>2002</td>
<td>1</td>
<td>M</td>
<td>50</td>
<td>PD</td>
<td>T4N4M1</td>
<td>R2</td>
<td>SCC</td>
<td>Minor salivary</td>
<td>RT, S</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>2003</td>
<td>2</td>
<td>F</td>
<td>40</td>
<td>PD</td>
<td>T1N0M0</td>
<td>R1</td>
<td>SCC</td>
<td>Parotid</td>
<td>RT, S</td>
</tr>
<tr>
<td>Na et al.</td>
<td>2004</td>
<td>1</td>
<td>M</td>
<td>60</td>
<td>PD</td>
<td>T2N1M1</td>
<td>R0</td>
<td>SCC</td>
<td>Submandibular</td>
<td>RT, S</td>
</tr>
<tr>
<td>Yoon et al.</td>
<td>2005</td>
<td>2</td>
<td>F</td>
<td>50</td>
<td>PD</td>
<td>T3N1M1</td>
<td>R0</td>
<td>SCC</td>
<td>Minor salivary</td>
<td>RT, S</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>2006</td>
<td>1</td>
<td>M</td>
<td>70</td>
<td>PD</td>
<td>T1N2M1</td>
<td>R1</td>
<td>SCC</td>
<td>Parotid</td>
<td>RT, S</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>2007</td>
<td>1</td>
<td>M</td>
<td>60</td>
<td>PD</td>
<td>T2N3M1</td>
<td>R0</td>
<td>SCC</td>
<td>Submandibular</td>
<td>RT, S</td>
</tr>
<tr>
<td>Na et al.</td>
<td>2008</td>
<td>2</td>
<td>F</td>
<td>40</td>
<td>PD</td>
<td>T3N3M1</td>
<td>R0</td>
<td>SCC</td>
<td>Minor salivary</td>
<td>RT, S</td>
</tr>
<tr>
<td>Yoon et al.</td>
<td>2009</td>
<td>1</td>
<td>M</td>
<td>70</td>
<td>PD</td>
<td>T4N4M1</td>
<td>R2</td>
<td>SCC</td>
<td>Parotid</td>
<td>RT, S</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>2010</td>
<td>1</td>
<td>M</td>
<td>60</td>
<td>PD</td>
<td>T2N1M1</td>
<td>R0</td>
<td>SCC</td>
<td>Submandibular</td>
<td>RT, S</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>2011</td>
<td>2</td>
<td>F</td>
<td>40</td>
<td>PD</td>
<td>T3N3M1</td>
<td>R0</td>
<td>SCC</td>
<td>Minor salivary</td>
<td>RT, S</td>
</tr>
</tbody>
</table>

NA = not assessed, RT = radiotherapy, S = surgery, Ned = no evidence of disease, DUD, died of unrelated disease, DOD = died of disease, AD = alive with disease, PG = parotid gland, SMG = submandibular gland, MSG = minor salivary gland
### TABLE 2 SUMMARY OF THE PATIENTS WITH CAUCASIAN ORIGIN ONLY

<table>
<thead>
<tr>
<th>N</th>
<th>Author [ref]</th>
<th>Year</th>
<th>n</th>
<th>LEC cases</th>
<th>Caucasian (n)</th>
<th>Age (mean)</th>
<th>Gender</th>
<th>Site</th>
<th>tumor size (cm)</th>
<th>Treatment</th>
<th>Follow-up (mean)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rudanovic C et al</td>
<td>1981</td>
<td>1</td>
<td>1</td>
<td>35</td>
<td>m</td>
<td>PG 2</td>
<td>na</td>
<td>1a</td>
<td>na</td>
<td>29</td>
<td>AD</td>
</tr>
<tr>
<td>2</td>
<td>Asan et al</td>
<td>1984</td>
<td>1</td>
<td>1</td>
<td>86</td>
<td>f</td>
<td>SMG 5</td>
<td>na</td>
<td>1a</td>
<td>na</td>
<td>29</td>
<td>NED</td>
</tr>
<tr>
<td>3</td>
<td>E.K. Kott et al</td>
<td>1994</td>
<td>3</td>
<td>2</td>
<td>46</td>
<td>11</td>
<td>PG 6</td>
<td>na</td>
<td>3a</td>
<td>na</td>
<td>70</td>
<td>NED</td>
</tr>
<tr>
<td>4</td>
<td>Lam et al</td>
<td>1991</td>
<td>6</td>
<td>1</td>
<td>55</td>
<td>1</td>
<td>PG 6</td>
<td>na</td>
<td>3a</td>
<td>na</td>
<td>70</td>
<td>NED</td>
</tr>
<tr>
<td>5</td>
<td>Hammons-Dickson SJ et al</td>
<td>1991</td>
<td>13</td>
<td>2</td>
<td>53</td>
<td>1</td>
<td>PG 6</td>
<td>na</td>
<td>1a</td>
<td>neg</td>
<td>70</td>
<td>NED</td>
</tr>
<tr>
<td>6</td>
<td>Korcas et al</td>
<td>1995</td>
<td>2</td>
<td>2</td>
<td>62</td>
<td>4</td>
<td>PG 6</td>
<td>na</td>
<td>1a</td>
<td>pos</td>
<td>70</td>
<td>NED</td>
</tr>
<tr>
<td>7</td>
<td>Korcas et al</td>
<td>1996</td>
<td>1</td>
<td>1</td>
<td>64</td>
<td>4</td>
<td>MCG 2</td>
<td>na</td>
<td>1a</td>
<td>pos</td>
<td>70</td>
<td>NED</td>
</tr>
<tr>
<td>8</td>
<td>Korcas et al</td>
<td>1997</td>
<td>1</td>
<td>1</td>
<td>69</td>
<td>4</td>
<td>PG 6</td>
<td>na</td>
<td>1a</td>
<td>pos</td>
<td>70</td>
<td>NED</td>
</tr>
<tr>
<td>9</td>
<td>Korcas et al</td>
<td>2001</td>
<td>2</td>
<td>2</td>
<td>64</td>
<td>4</td>
<td>PG 6</td>
<td>na</td>
<td>1a</td>
<td>pos</td>
<td>70</td>
<td>NED</td>
</tr>
<tr>
<td>10</td>
<td>Wu et al</td>
<td>2002</td>
<td>1</td>
<td>1</td>
<td>54</td>
<td>1</td>
<td>PG 6</td>
<td>na</td>
<td>1a</td>
<td>pos</td>
<td>70</td>
<td>NED</td>
</tr>
<tr>
<td>11</td>
<td>Balarie I et al</td>
<td>2004</td>
<td>2</td>
<td>2</td>
<td>55</td>
<td>1</td>
<td>PG 6</td>
<td>na</td>
<td>1a</td>
<td>pos</td>
<td>70</td>
<td>NED</td>
</tr>
<tr>
<td>12</td>
<td>Hermann et al</td>
<td>2007</td>
<td>1</td>
<td>1</td>
<td>67</td>
<td>1</td>
<td>PG 6</td>
<td>na</td>
<td>1a</td>
<td>pos</td>
<td>70</td>
<td>NED</td>
</tr>
<tr>
<td>13</td>
<td>Mavraganas et al</td>
<td>2007</td>
<td>1</td>
<td>1</td>
<td>67</td>
<td>1</td>
<td>PG 6</td>
<td>na</td>
<td>1a</td>
<td>pos</td>
<td>70</td>
<td>NED</td>
</tr>
<tr>
<td>14</td>
<td>Holz et al</td>
<td>2013</td>
<td>1</td>
<td>1</td>
<td>32</td>
<td>1</td>
<td>PG 6</td>
<td>na</td>
<td>1a</td>
<td>pos</td>
<td>70</td>
<td>NED</td>
</tr>
</tbody>
</table>

**Note:** A = Alive, D = Died, NED = Not evaluated during follow-up, NA = Not available.
VI DISCUSSION

We added a case of a LEC in an MSG to 404 cases found in a review of the English literature.

To our knowledge it is the first literature review focusing on LEC of the MSG. We found only 18 patients out of 405 with Caucasian origin (5%).

As many of the 33 reports were focused on histopathological features of the entity, clinical information turned out very limited. In only 21% of the 33 reports (84 cases), clinical information on the treatment and outcome were available. The 2 publications with the most patients (Saku et al., Tian et al.) are from Asian countries and did not provide the required clinical information to estimate the potential value of postoperative radiation.

In the literature, a slight prevalence of the LEC has been suggested for the female sex [35] which is presented as well in our patients of Caucasian origin; 12/18 patients are female (66%). The publication of Saku et al (n =160) could not show a female predominance, therefore Tian et al (n= 106) published female cases twice as many as male cases.

Based on the reported provided details, only our own patient was treated trimodally with postoperative radiotherapy.

It has been supposed that LEC even outside the nasopharynx is a radiosensitive disease [44]. Dubey et al at M.D. Anderson have published a retrospective review of 34 patients from 1950-1994 with nonnasopharyngeal LEC of the head and neck. In 2 of these patients the primary tumor site was the parotid gland, no further details for these 2 two cases were provided. The local control rate of this series was 94% after a median FU of 7.5 years, so the authors suggested irradiation of the primary tumor of patients with nonnasopharyngeal LEC of the head and neck.

The knowledge about LEC is mainly based on numerous literature of nasopharyngeal cancer. Wolff et al showed in 6 patients with LEC of the nasopharynx in patients treated with primary radio chemotherapy followed by adjuvant administration of interferon-beta for 6 months a 100 percent OS after FU of 5 years [45]. Buehrlen et al demonstrated a cure rate >90 % in 45 patients (age 8-20 years) after treatment with primary radio chemotherapy (60 Gy) and adjuvant interferon-beta [46].

Based on the available data, the question of whether or not it is appropriate to treat a patient with LEC of the parotid glands like a patient with LEC of the nasopharynx remains open.

Based on the limited clinical data available, the value of additional postoperative radiation therapy in LEC of the salivary glands remains unclear.

VII CONCLUSIONS

Based on the limited information available of the published reports the value of radiotherapy for patients with LEC of the parotid gland remains unclear.

REFERENCES


