HYBRID TUMOURS OF THE PAROTID GLAND – 7 YEARS' EXPERIENCE

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Abbreviations:

SCC - squamous cells carcinoma

CT - computed tomography

HTs - hybrid tumours

PG - parotid gland

MNs - malignant neoplasms

Abstract

Aims—Hybrid tumours (HTs) of the parotid gland (PG) are extremely uncommon. A review of the literature revealed that most reported cases were either a combination of two distinct benign neoplasms or a benign neoplasm and another malignant tumour. The limited number of reported HTs cases makes the prognostic evaluation and treatment selection difficult. Here, we report the literature review and our experience with HTs in the PG.

Methods and Material—The present study evaluated retrospectively 450 cases of the PG tumours, which were treated in our hospital. Out of 450 parotidectomies performed in 5 cases (1.1%) HTs were diagnosed on postoperative histopathology examination. Moreover the article includes a short review of the literature on hybrid neoplasms of the PG.

Results—Based on the literature review HTs have been described in less than 0.1% of all the PG tumours. Only 21 cases of hybrid malignant neoplasms (with our 2 cases) have been reported thus far in the literature. Three of 5 our HTs cases were diagnosed as benign HTs and 2 cases as malignant HTs. The most common component of tumours was a pleomorphic adenoma. In two cases it was combined with Warthin tumour and in one case with basal cell adenoma. Malignant HTs were composed of squamous cells carcinoma (SCC) and Burkitt lymphoma in the first case and polymorphous carcinoma and low grade lymphoma malignum lymphociticum in the second case. Thus we paid a special attention to these cases in the article and we present detailed medical history of these two cases.

Conclusions—The histogenesis of HTs is largely unknown. Recognition of HT is important particularly when the component tumours have different biological behaviour. However, the limited number of reported cases makes the prognostic evaluation and treatment selection difficult.

Keywords— hybrid tumours, hybrid neoplasms, synchronous neoplasms, parotid gland

1. Introduction

Parotid gland (PG) tumours comprise 3% of all head and neck tumours. Although uncommon, the 2005 WHO classification of salivary gland tumours recognizes 24 different malignant subtypes which present with different clinical courses and varying prognoses. Synchronous multiple unilateral tumours of the PG account for only 0.5% of all PG tumours [1-2]. The definition of hybrid tumours (HTs) is not clarified. Some authors used this terminology as a synonym for synchronous tumours, which is two separated simultaneous tumours occurring in one topographical region. Other, defined HTs as simultaneous occurrences of two or more histologically different types of neoplasms with identical origin within the same area. Based on our experience HTs must be distinguished from the multiple occurrences of salivary gland tumours which can develop syn- or metachronously. Thus, in this study we define HTs as two or more histologically different types of neoplasms in one tumour mass with a distinct transition zone (capsule or salivary gland tissue) between them, clearly confirmed by histopathology findings. In most of HTs cases, simultaneous tumours of PG are compound of two histologically distinct benign neoplasms. When it occurs, the most common combination is Warthin tumour and a pleomorphic adenoma. A few cases of combined benign and malignant HTs have been reported.

Here, we report our experience with HTs in PG. The present study aimed to investigate retrospectively the characteristics, as well as the clinical, radiological and laboratory features, and the treatment results in the patients hospitalized in our department because of HTs. To the best of our knowledge, one of these cases is the first report of a Burkitt lymphoma in PG and the first report of a HT composed of squamous cells carcinoma (SCC) and malignant lymphoma in this organ. We discuss the clinics of these cases and provide the literature review.

2. Material and Methods

To our knowledge, only 13 reports (19 cases) of hybrid malignant neoplasms (MNs) have been described until now (**Table 1-2**).

Table 1. Clinical findings of hybrid tumors in parotid gland: review of literature.

Case no.	Reference	Year	Age (years)	Gender	Size (cm)	Therapy	Follow-up (mths)
1	Seifert[19]	1996	53	M	6x3x2	TP	-
2	Ballestin[2]	1996	67	F	5,5	TP	NED (at 8mths)
3	Croitoru[7]	1999	53	M	6x4.5x3.5	SR RT	NED
4			71	M	2.9	SR RT	NED
5			28	M	2.5x2	SR RT	AWD
6	Chetty[5]	2000	58	M	2.5	PP	-
7	Zardawi[21]	2000	78	F	4.5x4x3	TP	-

8	Nagao[14]	2002	74	F	10	TP RT	NED (at 10mths)
9			56	M	2	SP RND RT	NED (at 31mths)
10			73	F	2	SP	NED (at 48mths)
11			40	M	3	SP RT	NED (at 180mths)
12			65	M	5	TP RND RT	AWD (at 4mths)
13			42	M	4	SP	-
14			66	M	3.5	TP RND RT	AWD (at 20mths)
15	Piana[16]	2004	-	F	4	TP RND RT	NED (at 6mths)
16	Murphy[13]	2006	68	F	4x4x3	TP	DOC (at 5mths)
17	Kainuma[12]	2010	74	M	-	SP	NED (at 16mths)
18	Atay[1]	2014	71	M	-	-	-
19	Sabri[17]	2014	51	M	11x14x6	TP RT	-
20	Our case 1	2015	77	M	3.5x3x5	SR RND RT CHT	DOC (at 12mths)
21	Our case 2	2015	83	M	10x3x4	SR RND RT CHT	-

M:male, **F**:female, **TP**:total parotidectomy, **SR**:surgical tumore resection, **RT**:radiotherapy, **CHT**: chemotherapy, **PP**:partial parotidectomy, **RND**:radical neck dissection; **SP**:superficial parotidectomy, **NED**:no evidence of disease; **AWD**:alive with disease; **DOC**:died of other causes, **mths:**months;

Table 2. Histology of hybrid tumours in parotid gland– literature review

Histologic diagnosis	Case no.																					Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Salivary duct carcinoma	+					+		+				+	+	+	+			+	+			9
Epi-myoepithelial cell carcinoma					+	+	+		+	+	+					+		+	+			9
Adenoid cystic carcinoma				+	+			+				+					+					5
Acicnic cell carcinoma	+	+						+						+								4
Basal cell carcinoma									+	+							+					3
Mucoepidermoid carcinoma		+		+			+															3
Squamous cell carcinoma			+								+				+					+		4
Low-grade polymorphous carcinoma													+								+	2
Lymphoepithelial carcinoma																+						1
B-cell Lymphoma (Burkitt lymphoma)																				+		1
Lymphoma malignum lymphociticum																					+	1
Fibrosarcoma			+																			1

The present study evaluated retrospectively 450 cases, which were treated in our hospital because of PG tumour between January 2007 and December 2014. Out of 450 parotidectomies performed during this period in 5 cases (1.1%) HTs were diagnosed on postoperative histopathology examination. In 3 cases we performed superficial parotidectomy according to clinical characteristic indicating benign neoplasm as well as slowly progressing asymptomatic tumour. In other two cases we observed the fast-growing tumour with a facial nerve dysfunction and the malignant cells suspicion on the fine needle aspiration thus total parotidectomy was performed.

3. Results

From 2007 to 2014, 450 cases of PG tumours were operated in our hospital. Of those, 3 (0.66%) cases were diagnosed as benign HTs and 2 (0.44%) cases as malignant HTs. With regard to histopathology results, the most common component of tumours was a pleomorphic adenoma which was noticed in each benign HT. In two cases it was combined with Warthin tumour and in one case with basal cell adenoma. In the next 2 cases HT was composed of malignant neoplasms (MNs), thus we paid a special attention to these cases in the article and we present below detailed medical history of these two cases. The final pathological diagnosis of two malignant HTs were SCC and Burkitt lymphoma in the first case and polymorphous carcinoma and low grade lymphoma malignum lymphociticum in the second case.

The age of all patients with PG tumours ranged from 7 to 94 years with the mean age of 53± 18 years. Peak incidence for HTs of PG was between seventh and eight decades of life. With regards to gender distribution of PG tumours, 43.1% were male and 56.9% were female. The male to female ratio was 1:1.3. Among the HTs there was significant predominance of male and the most common effected side was the right PG - in 4/5 cases. Comparing the mean period between occurrence of the first symptoms and parotidectomy the similar time in both hybrid and single benign neoplasms were observed. Similar, significantly shorter but same period for single and hybrid MNs was observed. In both malignant cases we observed fast - progressing facial nerve dysfunction. In all HTs cases preoperative USG and CT scan shown single tumour mass. In order to avoid postoperative misdiagnosis of PG tumour and overlook the HT it is vital to analyse the total tumour mass fastidiously. Considering that two our cases had a very rare HTs composed of two malignant entities with complicated diagnosis and treatment we describe them in details below.

3.1.CASE 1:

A 77-year-old male patient presented with a deforming right hemifacial mass growing since 6 months, measuring 3.9x3.5 cm. Of note is that six months before the PG tumour occurred the patient underwent excision of the right auricle tumour (histopathology: basal cell carcinoma (BCC) was totally removed). On physical examination immovable mass was palpated in the right PG region. Furthermore, there was marginal paresis of temporal-zygomatic branch of facial nerve. No enlarged cervical lymph nodes were palpated. Fine needle aspiration biopsy of the PG tumour disclosed clusters of malignant cells which could equal to SCC. Salivary gland CT (computed tomography) scan demonstrated enlarged right PG with intraparotid cyst-like tumour with peripheral intensification in contrast-enhanced phase that adhered to mandible head. Additionally CT scan did not revealed pathological neck lymph nodes.

At our Department: The patient underwent an extended radical parotidectomy on the right side. The tumour mass infiltrating whole PG was separated from surrounding tissues. The

infiltration reached perichondrium of external acoustic meatus, zygomatic bone, temporomandibular joint and extended into the masseter muscle. Thus total parotidectomy with resection of all branches of facial nerve, resection of perinchondrium of external auditory meatus, zygomatic bone and temporomandibular joint and elective neck dissection of I-IV lymph nodes groups with following face lifting procedure was performed. The surgical specimens were sent for histopathological examination.

Pathology: macroscopically: PG with homogeneous, whitish tumour (3.5x3x5 cm) reached tissue's margins with thick-wall cyst inside (3x2 cm). Histologically, the tumour mass showed B-cell Non-Hodgkin Lymphoma - Burkitt lymphoma (**Figure 1**).

Neoplasm cells showed the translocation t(8;14)(q24.1;14q32) assayed by Fluorescence in situ Hybridization (FISH) with probes from the regions c-Myc (8q24.1) and IgH (14q32), expression: CD20, BCL-6, CALLA and differential expression of: IgM, BCL-2, MUM-1. KI 67 marker was almost in 100% of examined cells. The cyst displayed a histologically different appearance: SCC with keratosis infiltrated the fibrous tissue and PG. The final pathological diagnosis was HT (SCC and Burkitt lymphoma) of PG, because of two distinctly different neoplasms in same topographic area with a single mass and a distinct transitional zone between two different malignant components (**Figura 2-3**).

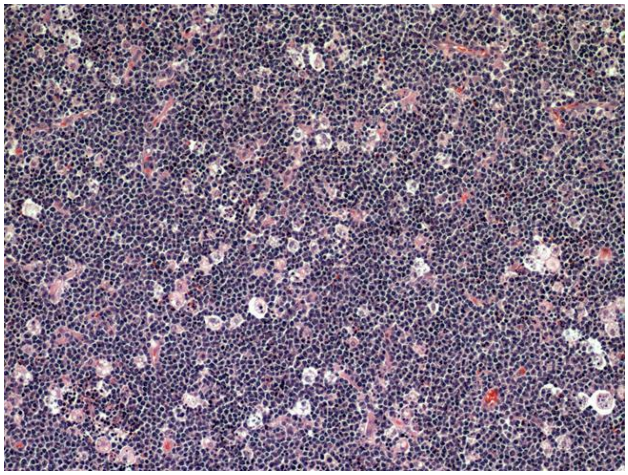

Figure 1. Microscopy: showed salivary gland parenchyma with infiltrating malignant neoplasm – Non- Hodgkin lymphoma Burkitt- like type. Immunohistochemistry confirmed extranodal lymphoma of parotid gland (H&E stain, original magnification 100x).

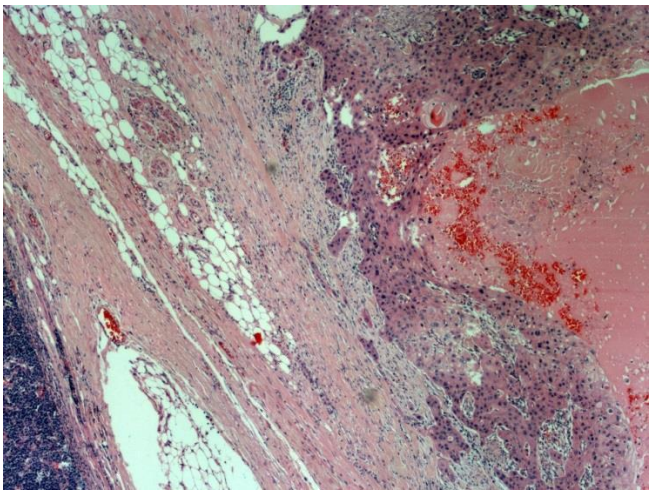

Figure 2. Received salivary gland tissue with tumour. Histologically, two distinctly different neoplasms in same topographic area with a single mass and a distinct transitional zone between two different malignant components. The tumour mass showed Burkitt lymphoma and the cyst displayed a histologically different appearance: SCC in low grade malignancy. (H&E stain, original magnification 40x).

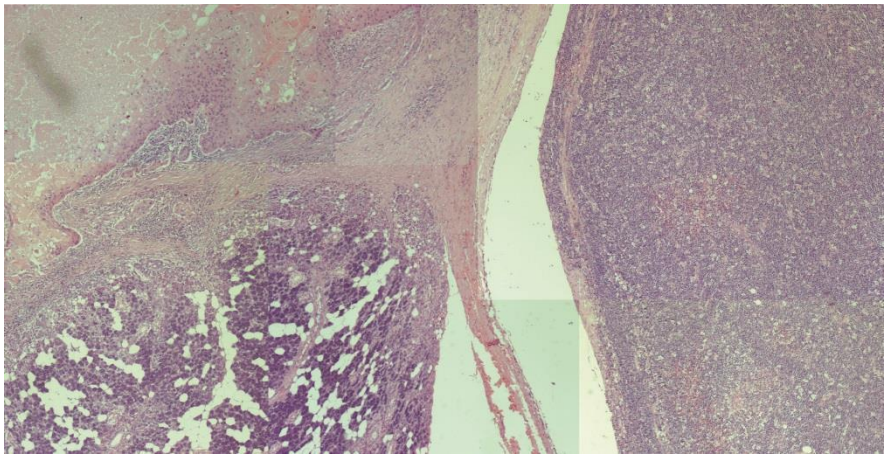

Figure 3. Microscopy combination of few pictures shows SCC, Burkitt lymphoma and salivary gland tissue.

The tumour had a cystic area and this region consisted of the SCC components with low grade malignancy. The histopathological surgical margin was tumour free and there were no metastases in lymph nodes.

Supplementary treatment: The supplementary treatment plan consisted of chemotherapy followed by radiation therapy to the primary site and right lateral neck area. Unfortunately 2 months after treatment, during follow-up examination, abdomen ultrasound revealed tumour – probably metastases in liver. The histological verification of this tumour hadn't been finished because of patient's death.

3.2.CASE 2:

A 83-year-old man presented with the history of right PG tumour growing progressively over a period of 12 months, measuring 3.0x6.0cm. The mass was firm, fixed with no overlying skin changes. The right facial nerve function was decreasing about 4 months to total facial nerve paralysis on admission (VI degree in House-Brackmann scale). Oral examination was unremarkable and fiber optic flexible laryngoscopy showed no narrowing of the pharyngeal walls. A fine needle aspirate revealed a picture suggesting malignant cells.

CT scan of the brain and neck showed 3.0x6.0x4.5 cm heterogeneously enhancing right PG tumour with areas of necrosis, involving the deep lobe of the PG. It was invading the right mandibular angle with bone erosion. Moreover, CT scan showed enlarged pathological I-V lymph nodes groups on the right side. The additional diagnostic imaging excluded distant metastasis.

At our Department: The patient underwent an extended radical parotidectomy on the right side with resection of all branches of facial nerve, partial resection the mandible, the right side radical neck dissection and following face lifting procedure. The surgical specimens were sent for histopathological examination.

Pathology: macroscopically: PG with homogeneous single tumour mass (10x3x4cm). Histologically, the tumour mass was composed of two components: polymorphous carcinoma and low grade lymphoma malignum lymphociticum. In the literature, there are numerous criteria used to define primary PG lymphoma **(Table 3).**

Table 3. Criteria used to define primary parotid gland lymphoma (information from references [3, 9,11, 18, 20]).

Any lymphoma originating in either glandular nodes or glandular parenchyma, regardless of its association with autoimmune disease or its subsequent stage; must be initial clinical manifestation of lymphoma
Any lymphoma originating in glandular parenchyma as initial clinical manifestation of lymphoma
Any lymphoma not associated with autoimmune disease, benign lymphoepithelial lesion, or myoepithelial sialadenitis
Any lymphoma originating in glandular parenchyma, not associated with autoimmune disease
Any lymphoma originating either in glandular parenchyma or in glandular lymph node with invasion of parenchyma, in absence of detectable disease outside of parotid gland
Any lymphoma originating in glandular parenchyma in absence of extraparotid involvement at time of diagnosis

The author used the first of the criteria listed in table 3 to define primary PG lymphoma; the present case, accordingly, is classified as such. The surgical margin was tumour free but in few neck lymph nodes the infiltration of both polymorphous carcinoma and lymphoma malignum was observed. The diagnosis of a HT was made.

Supplementary treatment: Patient was scheduled for postoperative radiation and chemotherapy.

4. Discussion

Hybrid tumours are very rare tumours which are composed of two different tumour entities, each of which conforms with an exactly defined tumour category [12]. The literature review showed there is no clear definition for them. Most researchers agree with definition that the tumour entities of a HT have an identical tumour mass within the same topographical area but different types of neoplasms with a distinct transition zone between them [13, 14]. In contrast, biphasically differentiated tumours are a mixture of two cellular patterns with a corresponding term in the tumour classification (eg. epithelial-myoepithelial carcinoma or mucoepidermoid carcinoma). Hybrid tumours must also be distinguished from other pathology such as the syn-or metachronously developed multiple salivary gland neoplasms, collision tumours and differentiated carcinomas [13-14,16-17, 19] **(Table 4)**.

Table 4. Pathologies which could be misdiagnosed as hybrid tumors of salivary gland [19].

(1) synchronous and multiple recurrences of tumors that are composed of histologically distinct tumors presenting as separate nodules;
(2) malignancies arising from a pre-existing benign tumor, as in carcinomas ex mixed tumor;
(3) collision tumors in which two malignant tumors about each other but actually arise from separate primary sites,
(4) carcinomas with metaplastic change,
(5) differentiated carcinomas,
(6) sarcomatoid salivary duct carcinoma,
(7) adenosquamous carcinoma

In the tissue samples of salivary gland tumours recorded in the Salivary Gland Register (Institute of Pathology, University of Hamburg, Germany) between 1965 and 1994 HTs comprised less than 0.1% of all registered tumours [19]. In our material among the 450 PG tumours the histopathology results confirmed the HT diagnosis in 5 cases (1.1%). Three of them were composed of benign neoplasms, where adenoma pleomorphum was one of the component connected with Whartin adenoma (2 cases) and basall cell adenoma (1 case). We assume that the similar cellular origin of both types adenoma may be an explanation for its development in a hybrid adenoma.

Hybrid MNs in PG are extremely unusual that influence adversely both diagnostic and therapeutic problems and overall prognosis. Thus we described these cases details. Only 21 cases of hybrid MNs (with our 2 cases) have been reported thus far in the literature. Our results on malignant HTs review showed there was significant predominance of male – 15 on 21 cases. All patients underwent surgical resection of their tumours, extended with radical neck dissection in 5 cases. Twelve cases received postoperative radiotherapy and only in our cases additional chemotherapy was performed. The clinical follow-up was performed in 14 cases: 9 patients were alive with no evidence of disease, 3 patients were alive with recurrent disease, and 2 died 5 and 12 months after diagnosis.

Concerning histological type of tissue in HTs the two cell types could have a similar histogenetic origin. Therefore, the development of both cell types in HT with two trends of differentiation is possible [21]. Sometimes HT could show a composition of two different epithelial structures in a varied mixture [14,16]. A literature review also showed the reports about a hybrid carcinoma whose two components had a similar histogenetical basis: epithelial-myoepithelial carcinoma and a glandular type of adenoid cystic carcinoma [19] or epithelial-myoepithelial carcinoma and salivary duct carcinoma [1, 12]. Both carcinomas were composed of variable proportions of duct-lining cells and myoepithelial cells. A very rare and unique HT example with two absolutely different components could be acinic cell carcinoma and salivary duct or mucoepidermoid carcinoma [2, 19] or our cases of cancers combined with lymphoma in one tumour mass.

Based on literature review various carcinomas have been described in HTs, but the most often malignant components of HTs were epi-myoepithelial cell carcinoma (10 cases), salivary duct carcinoma (9 cases), and adenoid cystic carcinoma (6 cases). The most frequent malignant HTs were compound of salivary duct carcinoma and acinic cell carcinoma or epi-myoepithelial cell carcinoma (3 cases in both couples). To the best of our knowledge HT of PG compound of SCC and lymphoma tissue has not been reported yet in the literature. Moreover, we describe

the first case of Burkitt type lymphoma in the PG. In particular primary malignant lymphomas of salivary glands are rare, comprising only 1.7% to 3.1% of all salivary neoplasms and 8% of all extranodal disease of the head and neck [3, 9, 11]. Primary SCC, also known as primary epidermoid carcinoma accounts for 1 to 2% of salivary malignancies. It is frequent misdiagnosed with high-grade mucoepidermoid carcinoma (MEC). Its diagnosis was excluded with histopathology special stains (PAS and mucicarmine). The SCC in salivary gland was confirmed as low grade (G1). In the literature review there were 2 cases of hybrid MNs of the PG where one of the component was SCC. In these cases the second component was epithelial-myoepithelial carcinoma and salivary duct carcinoma. The salivary gland SCC is defined as high-grade risk tumour according to the recommendations of the American Joint Committee on Cancer (AJCC) or the International Union on Cancer (UICC) [10]. Our cases were the combination of the two so rare histological neoplasms' types.

Differentiation of the two tumours is prognostically important especially if one or all of them are MNs. Although prognostic information is limited, it is suggested that the aggressiveness of HT is determined by the histologically higher grade component [7]. In all our cases USG and CT scan described one tumour in PG thus detailed estimation of the whole removed tumour mass was necessary to obtain the HT diagnosis.

5. CONCLUSIONS

The limited number of reported HTs cases makes the prognostic evaluation and treatment selection difficult. Here, we report the literature review and our experience with HTs in the PG based on analysis of 450 PG tumours treated in our hospital. We determined the prognostic evaluation and selected the treatment according to the histologically higher grade component of tumour, however prognosis for two malignant HTs was poor.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

ACKNOWLEDGEMENTS

We are grateful to all patients who participated in the study.

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