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Rare Radiation-Induced Hybrid Parotid Carcinoma - Clinical Case with a Detailed Immunohistochemical Analysis and a Literary Review

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Abstract

Hybrid parotid tumors are extremely rare neoplasms with a frequency of 0.1% -0.4% of all registered tumors. After childhood radiation for cancer or benign disease with a localization head and neck, surviving patients already in adulthood develop secondary radiation -induced parotid neoplasm. We present an extremely rare clinical case of a 69-year-old woman who, as a child at the age of 10, has been held telegamaterapy with Cobalt-60 (^{60} Co) up to total dose (TD) 54Gy in the nasopharynx and up to TD 50Gy in the bilateral cervico-supraclavicular lymph nodes for nasopharyngeal carcinoma. 59 years after the radiation healing, which has been alive, the patient is diagnosed with a hybrid parotid tumor consisting of two malignant tumors- Salivary duct carcinoma and a Basal cell parotid adenocarcinoma. For the first time in medical literature in English, we describe a radiation -induced hybrid parotid carcinoma, which is represented by a detailed immunohistochemical analysis of the two carcinoma components.

Keywords

Radiation-induced parotid tumor; Hybrid parotid carcinoma; Immunohistochemical analysis; Salivary duct carcinoma; Basal cell parotid adenocarcinoma

Introduction

Salivary gland hybrid tumour, first described in 1996, is a very rare neoplasm for which exact morphological criteria have not been universally agreed upon [1]. Hybrid Carcinomas (HCs) of the salivary gland are a recently defined and rare tumor entity, consisting of two histologically distinct

types of carcinoma within the same topographic location [2,3]. In the Seifert and Donath study, the frequency of salivary gland hybrid tumors was less than 0.1% of all registered tumours and from the Nagao et al./ 2002 study, the frequency reaches 0.4% [2,4]. In order to be defined as hybrid tumors, these rare and difficult for histopathological image analysis of parotid tumors require an Immunohistochemical (IHC) analysis of their two different carcinoma components. For the first time in English medical literature, we present a rare radiation -induced hybrid parotid carcinoma consisting of basal cell adenocarcinoma and salivary duct carcinoma.

Clinical Case

It is about a 69-year-old woman who, as a child at the age of 10, has conducted telegamatherapy with Cobalt-60 (^{60}Co) up to Total Dose (TD) 54Gy in the nasopharynx and up to TD 50Gy in the both cervico-supraclavicular lymph nodes for nasopharyngeal carcinoma. In June 2024, the patient noticed an increasing non -painful formation in the left parotid gland. CT of the head and neck / August 2024- Left parotid gland- A heterogeneous formation with dimensions 27mm x 31mm x 36mm and discrete calcifications showing intense contrast in the periphery with a hypodense center / probably necrosis /. Single submandibular lymph nodes on the left with a diameter of 10 mm. Expressed calcinosis of the carotid arteries bilaterally, more in the left. Nasopharynx, oropharynx, hypopharynx and larynx with normal depiction. Head and neck MRI detects post -contrasting heterogeneous lesion enhancement in the left parotid gland with lobulated contours and sizes 27 mm x 36 mm. On the left submandibular, an enlarged lymph node measuring 17mm x 12mm is reported. Intraoperatively- In the left parotid gland a tumor is visualized, motionlessly linked to the proper skin. The formation was removed with the mandibular parotid lobe, and subsequently removed the temporal and pharyngeal lobe of the gland, which were infiltrated by the tumor process. In the second A and second B cervical level, 7 enlarged lymph nodes were found, which were carefully removed. Histological result- A major tumor with a mandibular lobe of the parotid gland.- Salivary gland, underlying soft tissues and skin with infiltration of tumor with nesting structure and comedo-like necrosis, composed of cells with copious eosinophilic cytoplasm and large nuclei with pronounced polymorphism and prominent nucleoli. Multiple focuses with perineural invasion **(Figure 1)** are observed.. It is found on the Baseloid tumor component represented by smaller cells with hyperchromatic nuclei and pale cytoplasm **(Figure 2)**, as well as focuses of intraductal (in situ) component, including with carceryization of acins. Resection lines are close to a wide area and are engaged in separate focuses. The presence of venous vascular invasion **(Figure 3)**. In 5 lymph nodes from the dissected 7 lymph nodes, carcinoma metastases **(Figure 4)** are reported. The temporal lobe of the gland does not take into account tumor infiltration, but in the frontal lobe the parenchyma and surrounding soft tissues are infiltrated by the carcinoma without affecting the adjacent lymph node. Immunohistochemistry (IHC)- Tumor tissue with nesting structure composed of basaloid cells with mild to moderate nuclear atypia and scarce cytoplasm, healine deposits among tumor nests with IHC expression for p40, CK 7, CK5/ 6 and S100 (from 20% cells) **(Figure 5 and 6)**. Lack of IHC reaction for EMA, androgen receptor (AR), MUC2 and MUC5 **(Figure 7)**. Infiltrative tumor nests consisting of cells with large vesicular nuclei, prominent nucleoli with profuse colorless basophilic cytoplasm **(Figure 8)** with positive IHC

expression of CK7, AR, EMA and HER2, MUC5/in 30% of cells **(Figure 9)** in the absence of a reaction of p40, CK 5/6, S100 protein and Muc2 **(Figure 10)**. An infiltrative tumor composed of solid nests with comedo-like necrosis in the largest nests. Among the stroma is partially preserved parotid ducts with a multiepitelial layer **(Figure 11A)** with positive IHC expression of p40 and CK 5/6, as well as an epithelial layer with positive expression of CK 7 **(Figure 11B-E)**. On the periphery of infiltrative nests on some places there are less cells with scarce cytoplasm and hyperchromic nuclei **(Figure 12A)**. Positive IHC expression in single cells of p40, CK 5/6, CK 7 and EMA **(Figure 12B-E)**, with a negative reaction to the S100, AR, MUC2 and MUC5 **(Figure 13)**

Pathohistological diagnosis

Hybrid parotid tumor consisting of two carcinomas-basal cell adenocarcinoma and salivary duct carcinoma with a maximum size of 2.5 cm with perineural and lymphovascular invasion and metastases in 4 of 7 dissected lymph nodes. Resection lines engaged- pT4 pN2b.

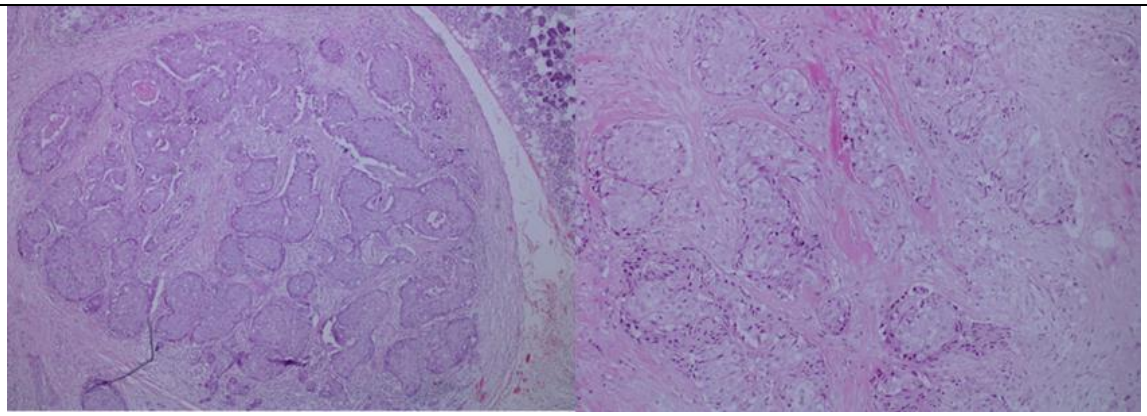

Figure 1: Salivary gland, underlying soft tissues and skin with infiltration of tumor with nesting structure and comedo-like necrosis, composed of cells with eosinophilic cytoplasm and large nuclei with pronounced polymorphism and prominent nucleoli. Multiple focuses with perineural invasion A/ Salivary duct carcinoma x 50; B/ Salivary duct carcinoma x 200.

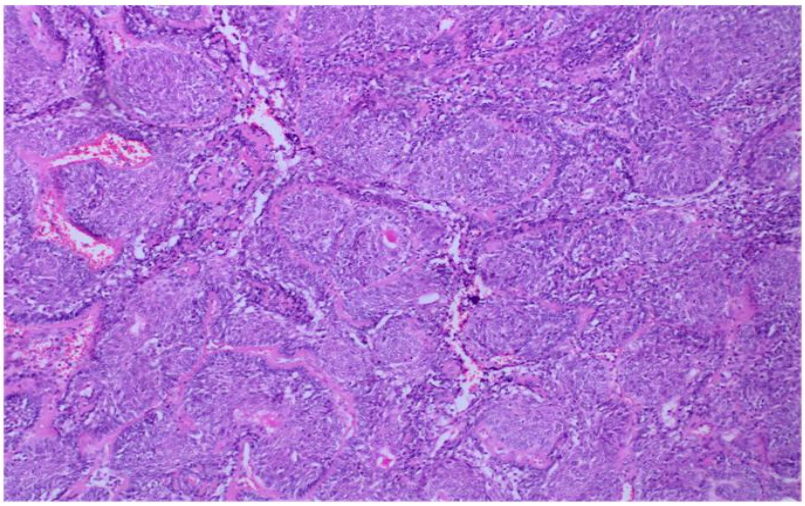

Figure 2: Basal cell adenocarcinoma- Basaloid tumor component represented by smaller cells with hyperchromatic nuclei and pale cytoplasm HEx100.

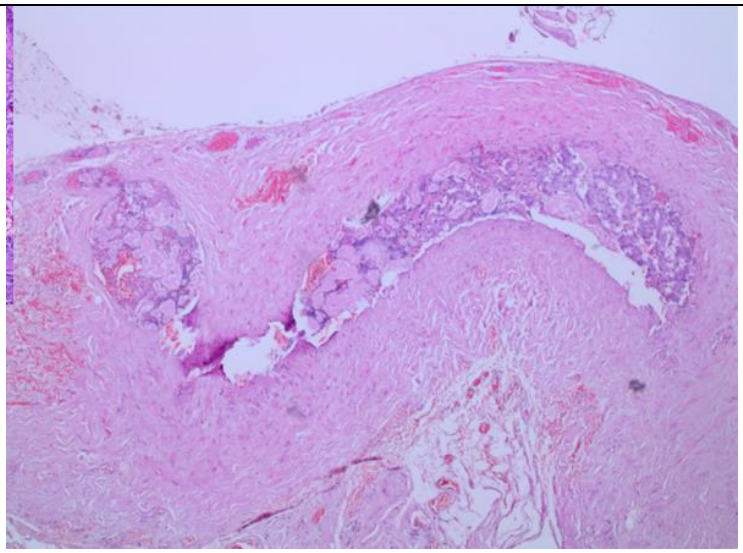

Figure 3: Salivary duct carcinoma – The presence of venous vascular invasion HE x 100.

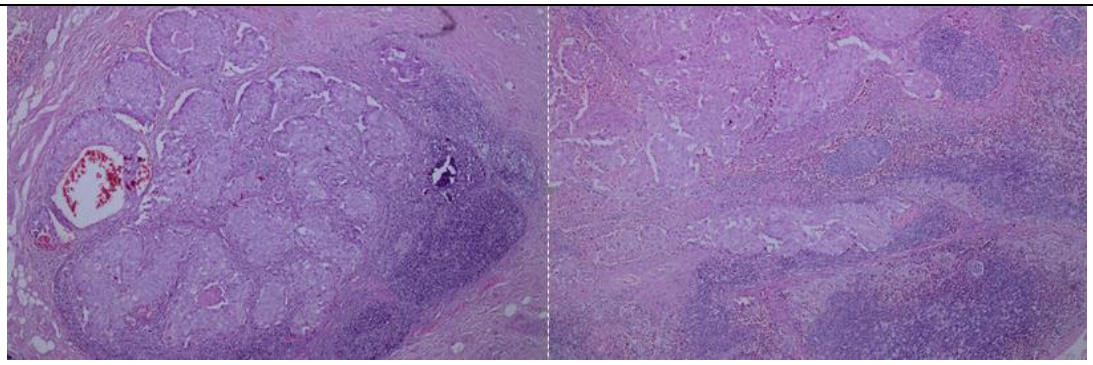

Figure 4: Salivary duct carcinoma -Lymph node metastasis A/B HE x50.

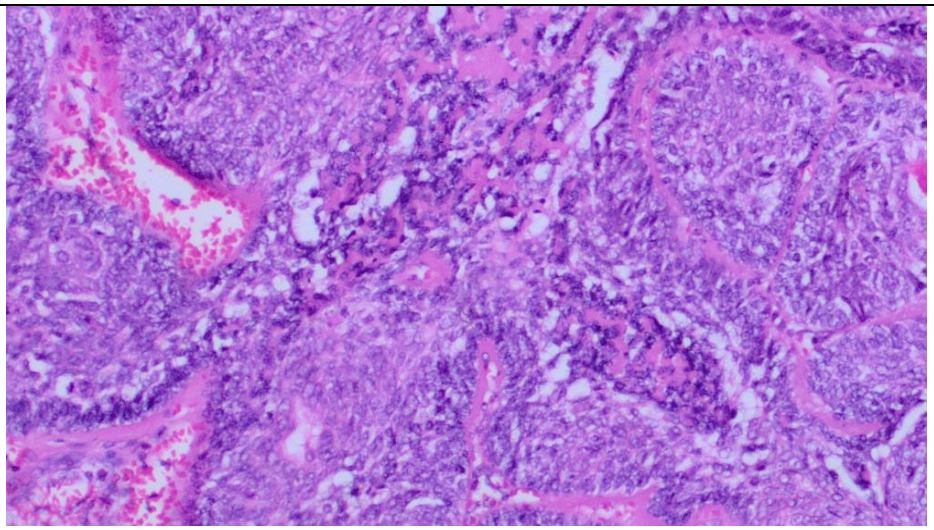

Figure 5: Basal cell adenocarcinoma -Tumor tissue with nesting structure composed of basaloid cells with mild to moderate nuclear atypia and scarce cytoplasm, healine deposits among tumor nests /HE x 200.

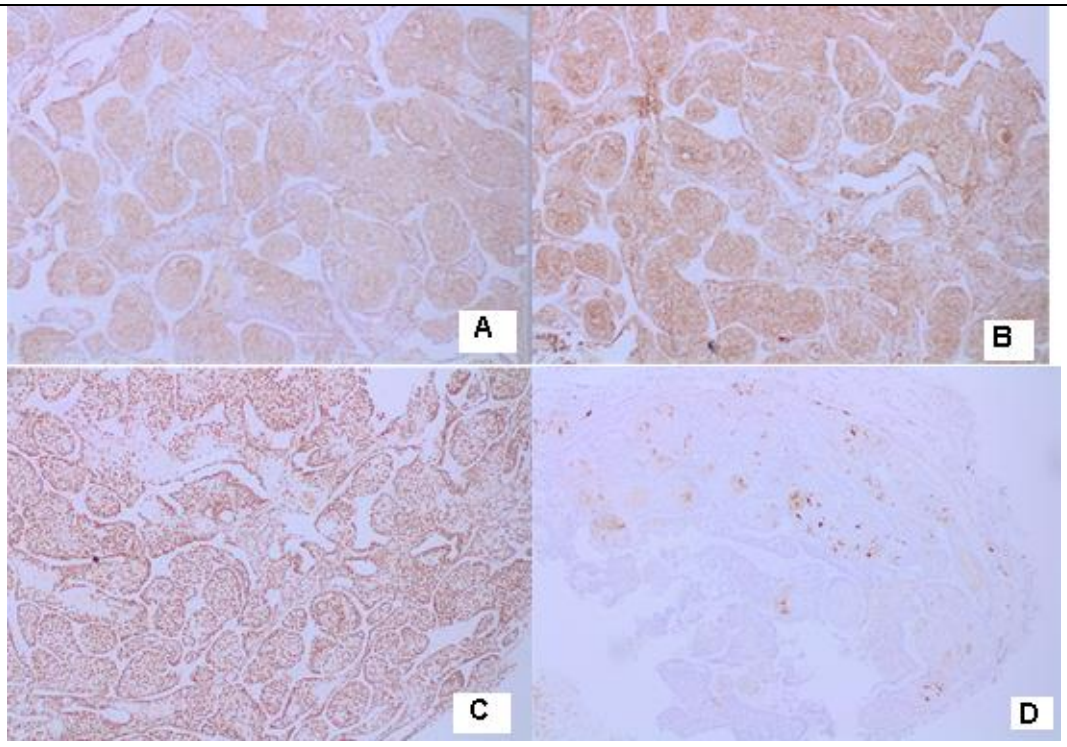

Figure 6: Basal cell adenocarcinoma -Positive IHC expression of: A/CK 5/6; B/ CK7; C/p40; D/ S100 protein in 20% of tumor cells.

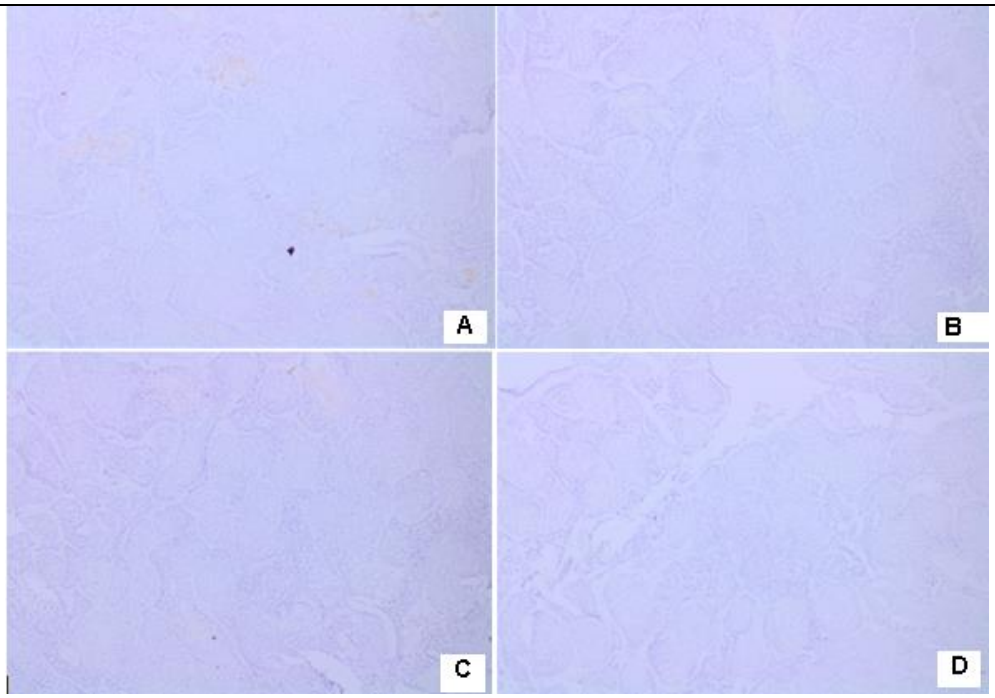

Figure 7: Basal cell adenocarcinoma- Negative IHC expression of: A/ EMA; B/ AR; C/ MUC2; D/ MUC5.

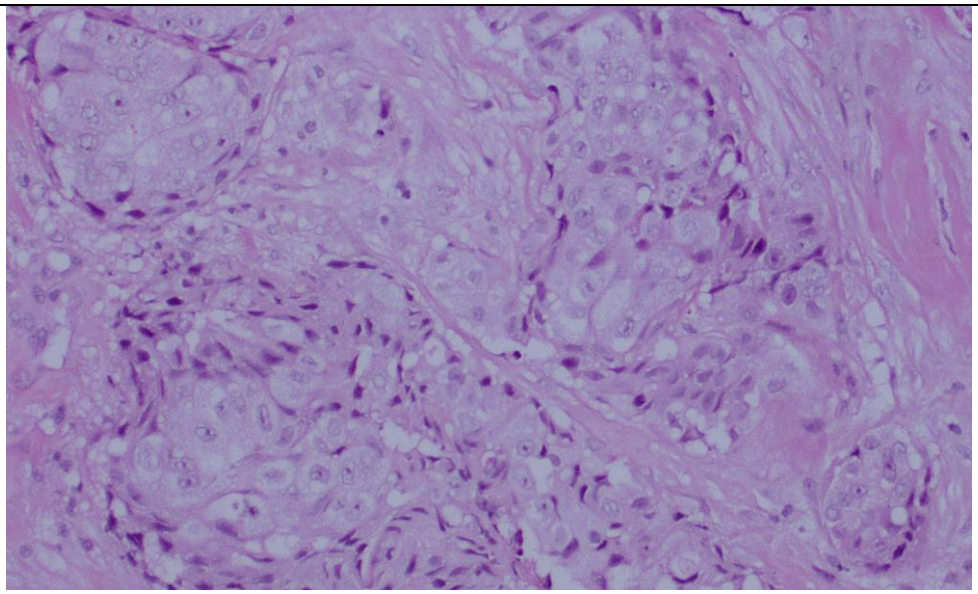

Figure 8: Salivary duct carcinoma - Tumor cells with large vesicular nuclei, prominent nucleoli with profuse colorless basophilic cytoplasm/ HE x 200.

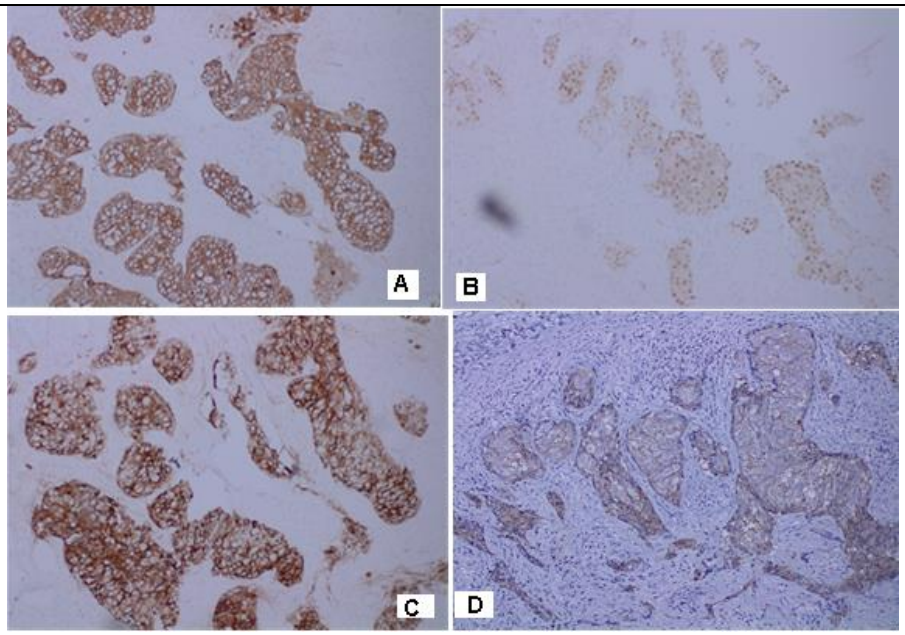

Figure 9: Salivary duct carcinoma- Positive IHC expression of: A/ CK7; B/AR; C/ EMA; D/HER2.

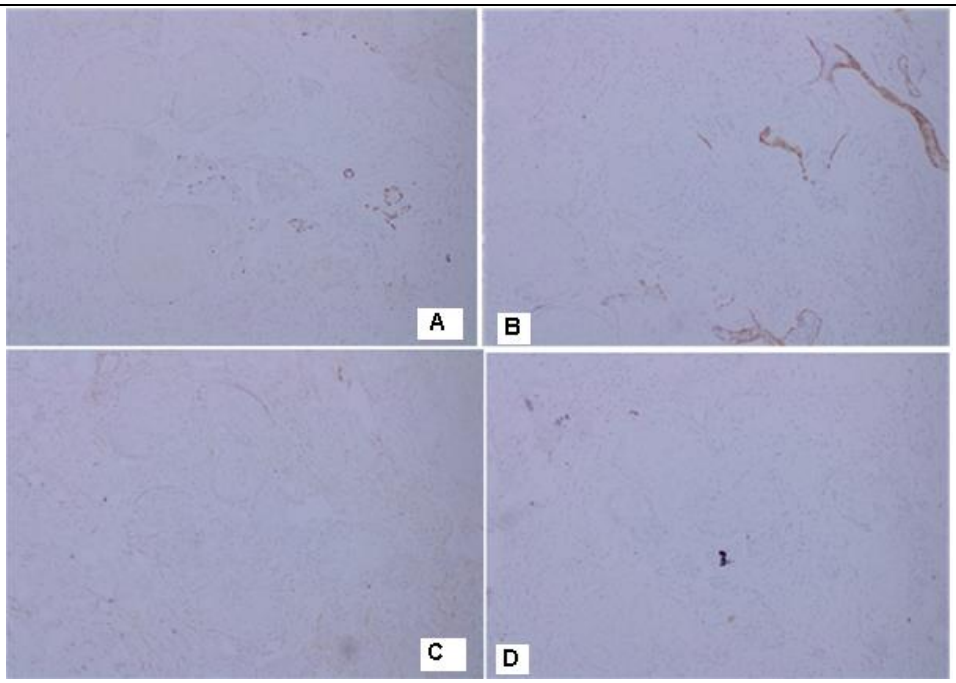

Figure 10: Salivary duct carcinoma – Negative IHC expression of: A/ p40; B/ CK 5/6; C/ S100 protein; D/ MUC2.

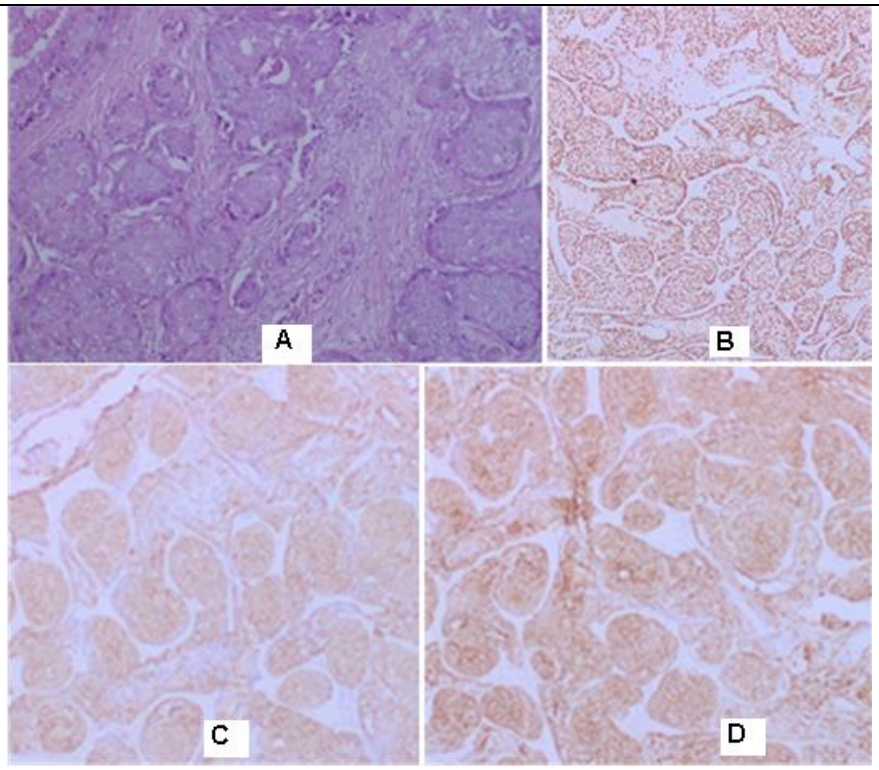

Figure 11: Partially preserved parotid ducts with a multiepitelial layer A/ HEx100; with positive IHC expression of: p40/B and CK 5/6/C, as well as an epithelial layer with positive expression of CK 7/D.

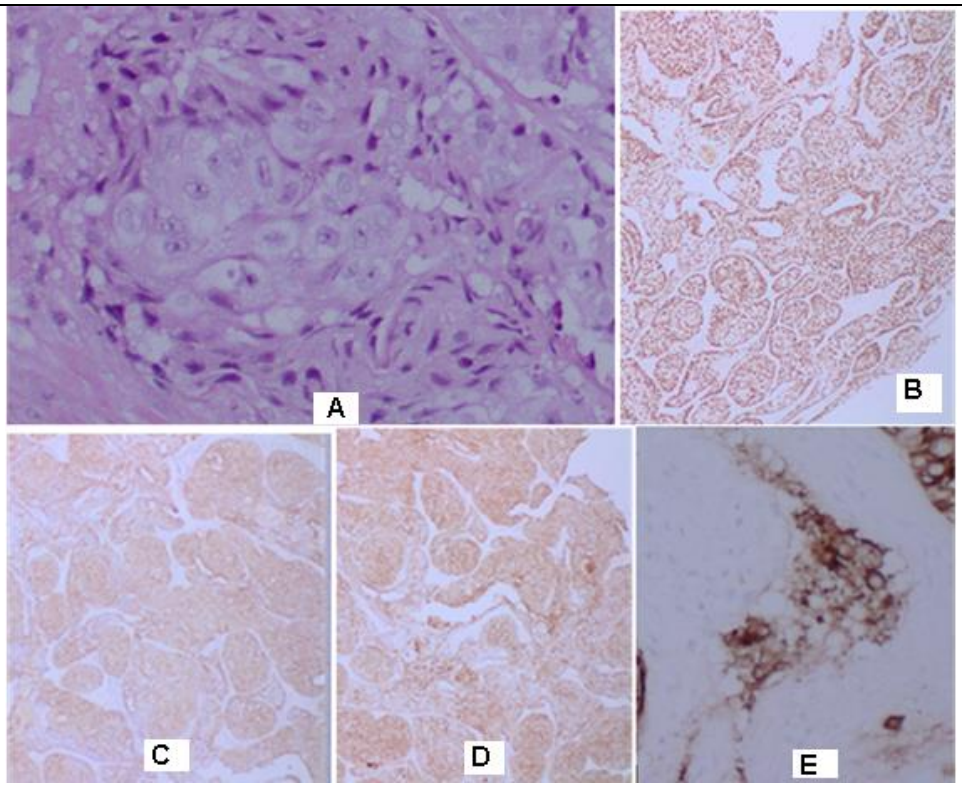

Figure 12: A/ On the periphery of infiltrative nests on some places there are less cells with scarce cytoplasm and hyperchromic nuclei/ HEx200 with positive IHC expression of; p40/ B; CK5/6/C; CK7/D and EMA/E.

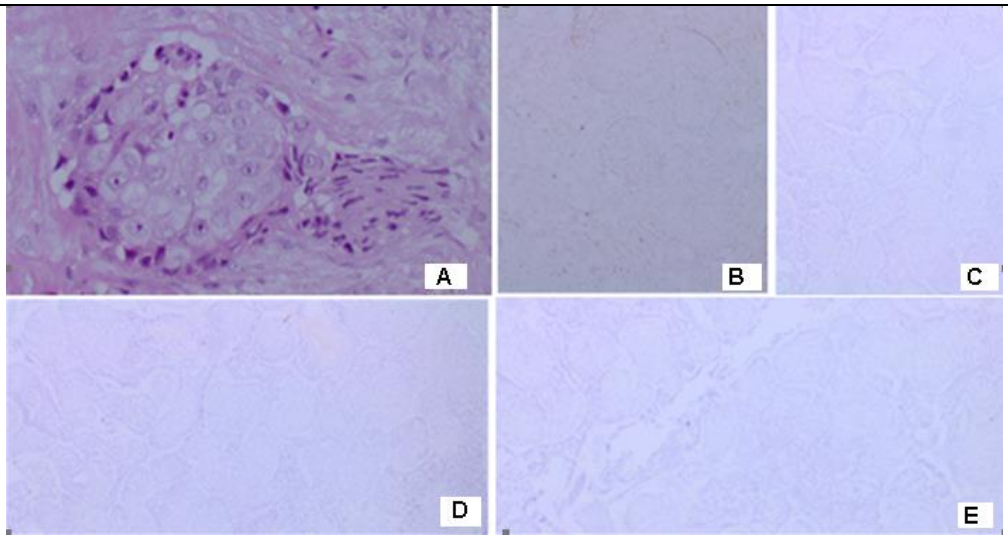

Figure 13: A/ On the periphery of infiltrative nests on some places there are less cells with scarce cytoplasm and hyperchromic nuclei /HE x200 with negative IHC expression of: B/ S100 protein; C/ AR; D/ MUC2 and E/ MUC5.

Due to the extremely aggressive Salivari duct carcinoma component, the available tumor necrosis, the presence of venous vascular invasion, tumor infiltration in the skin outside the parotid capsule (pT4) and metastases in 5 lymph nodes (pN2) **(Figure 3 and 4),** we have considered that the patient should have a postoperative

concurrent chemoradiotherapy. Due to fear and unpleasant memories of the past radiation, the patient categorically declined subsequent postoperative treatment, despite explaining that she was rescued by the nasopharyngeal carcinoma due to the irradiation performed in childhood.

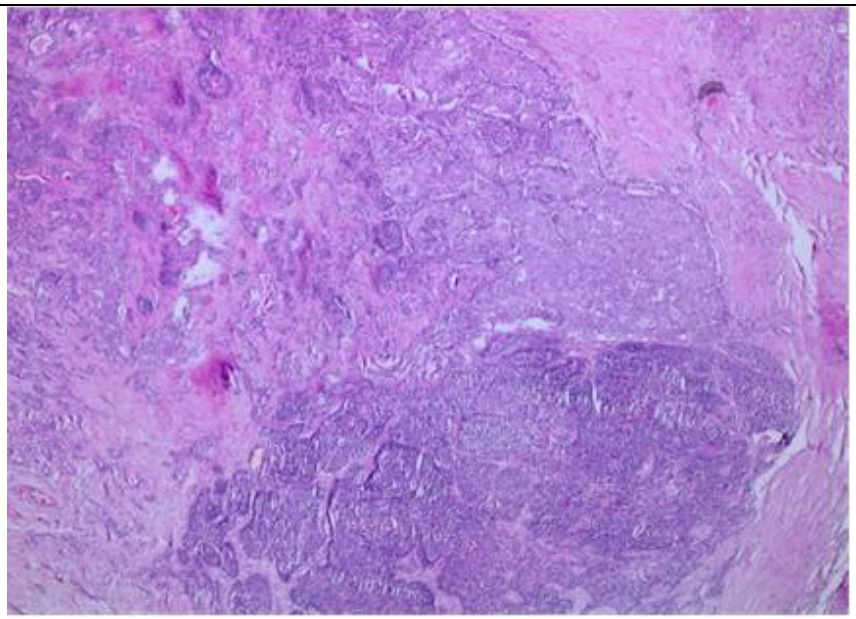

Figure 14: Ductal salivary carcinoma and Basal cell adenocarcinoma with an intervening transitional zone HE x 100.

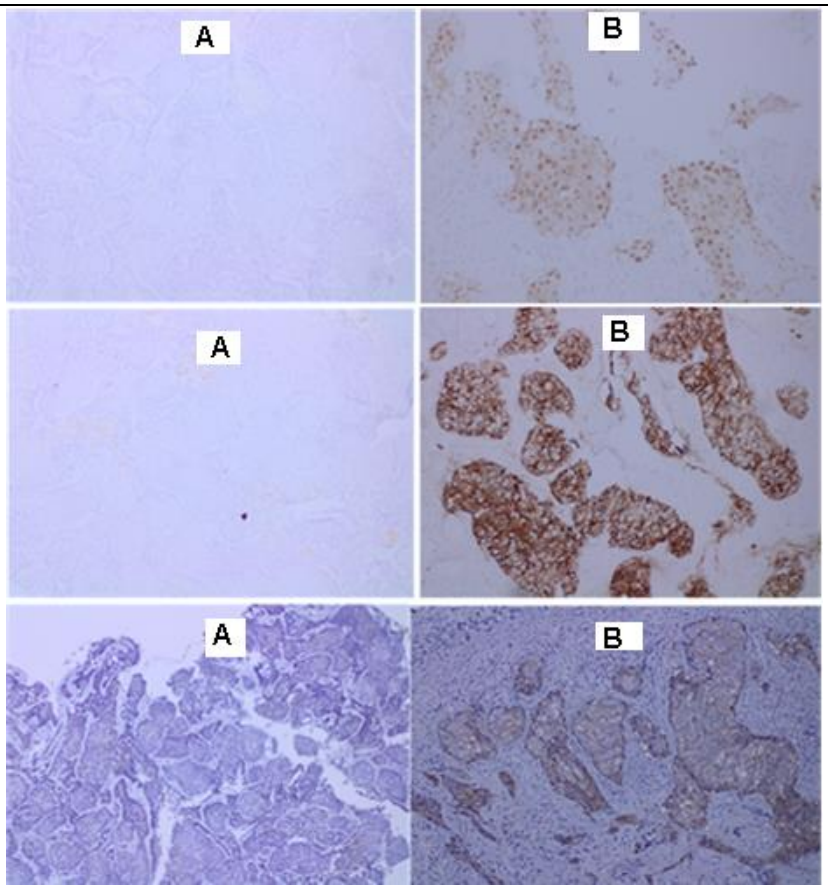

Figure 15: A/Basal cell adenocarcinoma- Androgen receptor negative B/ Salivary duct carcinoma Androgen receptor -positive x200; A/ Basal cell adenocarcinoma- EMA negative; B/ Salivary duct carcinoma – EMA positive x200; A/Basal cell adenocarcinoma- HER2 negative; B/ Salivary duct carcinoma – HER2 positive x200.

Discussion

Seifert and Donath [4] defined a new salivary gland tumor entity, characterized by containing two histologically distinct types of tumor within the same topographical area in a single mass [5], and proposed the term Hybrid Tumor (HT). Because Hybrid Carcinomas (HCs) arising in the salivary glands are rare, their clinicopathologic and immunohistochemical characteristics have not yet been well defined [2]. Gnepp et al. [6] proposed that in HCs, each element would differentiate toward distinctly different salivary elements. The most frequent malignant HCs were compound of salivary duct carcinoma and acinic cell carcinoma or myoepithelial cell carcinoma [7]. Chetty [8] suggested that completely divergent differentiation may lead to the appearance of two distinct tumor entities (hybrid tumors), whereas incomplete divergence may lead to tumors harboring overlapping histological features. In the literature "dedifferentiated" salivary gland carcinomas have sometimes been confused with HC [2], but they should be distinguished from each other from a clinicopathological point of view [9]. Due to the small number of cases reported, many of which lack follow-up details; indicators of prognosis of HTs are not available, but their behaviour seems to be similar to that of tumours with high-grade transformation [1]. The limited number of reported cases with hybrid parotid carcinomas makes the prognostic evaluation and treatment selection difficult [7]. Although prognostic information is

limited, it is suggested that the aggressiveness of HT is determined by the histologically higher grade componen **[10].** By 2013, 34 hybrid tumors were described in English medical literature, of which 2 in the submandibular salivary gland, 4 in palatum molle, 1 in the maxillary sinus, sublingual salivary gland and upper lip, and the remaining 25 tumors with parotid localization **[2,4,10-18].** These 25 hybrid parotid tumors lack our combination of the two carcinomas, namely Basal Cell Adenocarcinoma (BCAC) and Salivary Duct Carcinoma (SDC).

Our case is defined as hybrid parotid carcinoma, because in the same topographic region, two different and separating carcinomas, combined in one tumor mass, are displayed **(Figure 14).** This figure shows the transition zone between the different carcinomas, as Nagao T et al. refers to it, namely that, although both components were clearly separated from each other, a mixture of the two types of carcinoma formed an intervening transitional zone **[9].** Because some histopathological features of different salivary gland tumors overlap, Immunohistochemistry (IHC) is a valuable tool especially when used to delineate the two different carcinoma components of a HT **[15].** The different IHC expression of the two carcinomas presented shows a relatively well - differentiated BCAC and aggressively undifferentiated SDC **(Figure 15).** Basal cell adenocarcinoma component comprising relatively monomorphic atypical basaloid cells forming solid cell nests with apparent peripheral palisading arrangement **[3.12].** Due to their biologic behavior and prognosis, BCACs should be classified as low-grade carcinomas **[19].** In **Figure 2 and 5** is visualized tumor tissue with nesting structure composed of basaloid cells with mild to moderate nuclear atypia and scarce cytoplasm, healine deposits among tumor nests. **Figure 15** presents the main IHC differences in the expression of different markers in both carcinomas, namely the characteristic of SDC positive expression for the Androgen Receptor (AR), EMA and HER2 and negative for BCAC. **Figure 12** shows the basic histopathological characteristics with the relevant positive IHC expression at BCAC, namely expressing p40/ B; CK5/6/C; CK7/D and EMA/E. These basaloid adenocarcinoma tumor cells are IHC positive for the p40, a marker that is highly sensitive and specific for squamous cell carcinoma, as well as focal positive for the S100, the myepithelial marker required to identify the myoepithelial cell malignant tumor **(Figure 6).** BCAC tumor cells are IHC negative for the MUC2 and MUC5, markers that are used for differential diagnosis with mucoepidermoid parotid carcinoma **(Figure 7)** and with negative IHC expression of S100 protein/B and AR/C **(Figure 13).** Salivary Duct Carcinoma (SDC) is a rare, aggressive salivary malignancy **[20].** SDC is most frequently seen in men aged 50 or older **[21-23].** Though described as early as 1968, SDC was only recognized as a distinct tumor type by the World Health Organization (WHO) in 1991 **[24].** The diagnosis in a locally advanced stage, the high frequency of relapses and metastases in extra-regional lymph nodes are characteristic **[25-30].** SDC is the most aggressive tumor of the 21 subtypes of primary salivary gland carcinoma in the latest WHO classification, showing high rates of local recurrence and distant metastases **[31,32].** Exact pathohistological verification and differential diagnosis of this rare aggressive tumor requires IHC analysis of AR and HER2 expression. The diagnosis of SDC should be based primarily on the morphologic features with the support of AR immunohistochemistry **[33].** Infiltrative tumor nests consisting of cells with large vesicular nuclei, prominent nucleoli with profuse colorless

basophilic cytoplasm **(Figure 1 and 8)** with positive IHC expression of CK7, AR, EMA and HER2, MUC5/in 30% of cells **(Figure 9)** with negative reaction of p40, CK 5/6, S100 protein and Muc2 **(Figure 10).**

Why did we consider that the presented hybrid parotid tumor was radiation induced?

In 1948, Cahan **[34]** postulated the following criteria for radiation-induced malignancies: (1) the tumor must originate in the previously irradiated area; (2) there must be a sufficient time interval from irradiation and the onset of the secondary tumor; (3) the histology of the tumor must differ from the primary tumor; and (4) the patient must not have a condition favoring the development of tumors such as von Recklinghausen's disease or Li Fraumeni syndrome. Typically, RT-Induced Malignancies (RTIMs) are biologically aggressive cancers with a variable period of 5–10 years for hematologic malignancies and 10–60 years for solid tumors between RT and the development of the second cancer **[35].** According to their timing of onset, these RTIMs can be divided into four groups: acute (during RT), subacute (within weeks to months), delayed onset (within months to years), and much delayed onset (after several years) **[36].** From the world medical literature it is known that childhood radiation in the head and neck, even with small radiation doses, leads to radiation -induced carcinogenesis 77.6% occur in the parotid gland and 22.4% in the submaxillary and minor salivary glands **[37].** Forty -six percent of 26 patients with a previous history of irradiation for benign conditions of the abnormalities of the head and neck and salivary glands had one carcinoma and 11% had two carcinomas in the irradiated field. Eight of the 11 malignant tumors in these 26 patients were in the parotid gland **[38].** Salivary Gland Tumors (SGTs) account for about 6% of the second cancers and the majority of these are Mucoepidermoid Carcinomas (MEC) **[19,39,40].** Two children with diagnoses of intermediate-risk Acute Lymphoblastic Leukemia (ALL) at 22 months and 2 years of age were treated with multiagent chemotherapy and prophylactic cranial irradiation. 6 and 7 years after successful treatment, in the two grown children develops (MEC) **[41].** In 2012 Lauro, C.F. et al. for the first time in English medical literature, a radiation -induced oncocyte parotid carcinoma has been published **[42].** After the radiation of children with Hodgkin's disease has relationship between radiation exposure and subsequent development of SGTs. The median interval between radiation exposure and diagnosis was 21 years (range, 4-64 years) **[43].** It has been investigated the dose-response relationships for the incidence of SGTs in a cohort of 2945 children who were irradiated between 1939-1962. The mean dose to the salivary glands was 4.2 +/- 1.7 Gy. The majority (81 of 89) of the patients developed SGTs **[44].**

Conclusion

Hybrid parotid tumors are extremely rare neoplasms with a frequency of 0.1% -0.4% of all registered tumors. After childhood radiation for cancer or benign disease with a localization head and neck, surviving patients already in adulthood develop secondary radiation -induced parotid neoplasm. For the diagnosis of this radiation -induced hybrid parotid tumor a thorough IHC analysis of the two carcinoma components is required. Following a thorough review of medical literature in English about hybrid parotid tumors, as well as radiation -induced parotid neoplasms, we became convinced that this clinical case was the first described radiation -induced hybrid parotid carcinoma.

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