

## CASE REPORT

## A patient with pilomatricoma in the parotid region: case report and review of the literature

EDUARD MIHAI CIUCĂ<sup>1)</sup>, ALEX-IOAN SĂLAN<sup>1)</sup>, ADRIAN CAMEN<sup>1)</sup>, MARIUS MATEI<sup>2)</sup>, CĂLIN-GABRIEL ȘARLĂ<sup>3)</sup>, CLAUDIU MĂRGĂRITESCU<sup>4)</sup>

<sup>1)</sup>Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of Medicine and Pharmacy of Craiova, Romania

<sup>2)</sup>Department of Histology, University of Medicine and Pharmacy of Craiova, Romania

<sup>3)</sup>Department of Physical Education and Sports, "Vasile Goldiș" Western University, Arad, Romania

<sup>4)</sup>Department of Pathology, Faculty of Dentistry, University of Medicine and Pharmacy of Craiova, Romania

### Abstract

Pilomatricoma is a benign skin tumor originating from the matrix cells of the hair follicles. Sometimes, its diagnosis can be difficult, especially in the preauricular region, where in the differential diagnosis, in addition to other dermal and subcutaneous masses, primary and secondary parotid gland tumor lesions must be also considered. A 34-year-old female was referred to our Institution with a right preauricular swelling over 12 months, which enlarged in the last two months. The ultrasonography confirms the origin of the tumoral mass in the skin of the preauricular region and not from the superficial lobe of the right parotid gland. The patient underwent complete tumor excision and the histopathology and immunohistochemical exams confirmed the diagnosis of a conventional pilomatricoma evolving to a late regressive lesion. She was discharged considered as cured and no recurrences were reported within a period of eight months of follow-up. This is the first reported case in the last 30 years, in this location, in the Department of Oral and Maxillofacial Surgery our Institution. Regarding the rarity of these tumors, especially in this location, we must keep in mind to consider a broader differential diagnosis that includes both tumoral and non-tumoral skin lesion and also parotid gland lesions.

**Keywords:** pilomatricoma, immunohistochemistry, parotid region, skin neoplasm.

### Introduction

Pilomatricoma (pilomatrixoma; calcifying epithelioma of Malherbe) is a benign neoplasm of the hair follicle matrix cells. First described in 1880, as calcified epithelioma of sebaceous glands [1], it was named in 1961 as pilomatrixoma to emphasize its origin from the matrix of the hair follicles [2], and further on, in 1974, from phonetic reasons was modified to pilomatricoma [3].

Considered to be a rare skin tumor, it appears to be more common in children and young adults and frequently observed on the head and the upper extremities [4]. Clinically, typically presents as a solitary, asymptomatic, well-circumscribed and firm, subcutaneous tumor [5]. Usually, it is fixed to the overlying skin, which could be normal appearing or with a reddish or bluish tint, or even ulcerated [6]. They grow slowly, typically exhibiting between 0.5–3 cm in size or even larger, with more than 5 cm of maximum diameter, when it is designated as a giant tumor [7].

Histologically, the tumor is composed of solid nests of basaloid cells resembling the hair matrix cells which undergo abrupt trichilemmal-type keratinization becoming ghost cells [8]. Frequently, in the ghost cells areas are observed calcifications and foreign body reactions. Usually, the prognosis of patient with isolated pilomatricoma is good, but they do not spontaneously regress and some of these can become locally aggressive with a tendency to recur [9, 10]. Although rare, in literature it has been

reported the potential of its malignant transformation into a pilomatrix carcinoma [11, 12]. The conventional treatment is surgical excision, which in more aggressive tumors must be supplemented with safety excision margins of 1–2 cm to prevent recurrences [13].

We report a case of a right pre-auricular pilomatricoma developed in 34-year-old women from Dolj County (Romania) and we discuss the clinical and morphological peculiarities of this case. The written informed consent was obtained and the Institutional Ethics Committee approved this investigation.

### Case presentation

A 34-year-old female (D.A.I., Clinical Observation Form No. 5379/02.06.2017), resident of Craiova (a South-Western County in Romania) referred in February 2017 to our Institution (Emergency County Hospital of Craiova) with a right preauricular swelling, which started about one year ago and enlarged during last two months. Her past medical records showed grade 3 obesity and essential hypertension (stage 1).

### Local physical examination

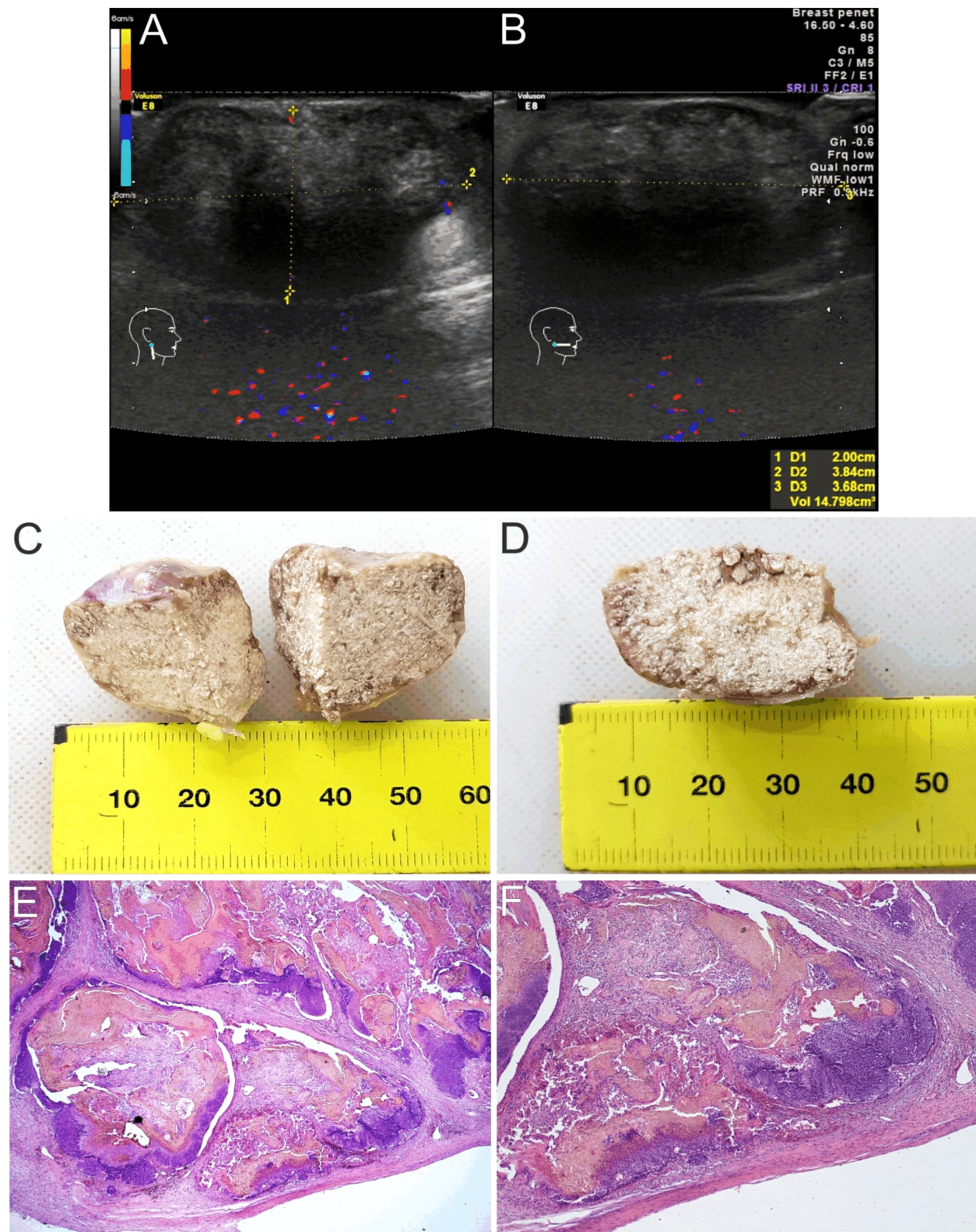
Physical examination confirmed a single, firm, painless, irregular mass which measured 4×3.5×2.5 cm, and which was freely mobile at its base into the right preauricular region. The overlying skin was stretched, with bluish

discoloration and fixed to the surface mass. There was no evidence of adenopathy, facial nerve dysfunction or mass drainage.

### Paraclinical investigations

The routine laboratory tests were in normal limits.

Ultrasonographic (US) investigation revealed a nodular, heterogeneous solid mass of about  $3.8 \times 3.7 \times 2$  cm (volume of  $14.8 \text{ cm}^3$ ), with multiple calcifications, hypoechoic capsule, located in the right preauricular region above the superficial lobe of parotid gland (Figure 1, A and B).



**Figure 1 – (A and B) Ultrasonographic aspect: nodular, heterogeneous solid mass with central multiple calcifications; (C and D) Gross aspect of the surgical specimen: round to oval, pseudo encapsulated mass, with a yellowish-white color, and calcifications in its central portion; (E and F) Nodulocystic lesion with a lobulated pattern, lined by a capsule consisting of dermal compressed fibrous tissue. HE staining: (E)  $\times 25$ ; (F)  $\times 50$ .**

## Initial management

Based on history, clinical, laboratory and imaging findings, a provisional diagnosis of right preauricular sebaceous cyst or a superficial lobe parotid tumor was considered. The tumor was excised by a pre-auricular incision, with preservation of the parotid gland, under general anesthesia, after a written informed consent was obtained. The wound was closed by primary intention and the healing was uneventful. After surgery, the patient received treatment with antibiotics, non-steroidal anti-inflammatory drugs and analgesic agents.

## Morphological examination

### Gross examination

The surgical specimen measured 4.5×4×3 cm, contained a round to oval, pseudo-encapsulated mass, with a yellowish-white color, calcifications in its central portion and areas with cheesy material that oozed out on cut section (Figure 1, C and D).

### Histopathological examination

After fixation and paraffin embedding, histological sections were stained using Hematoxylin–Eosin (HE), van Gieson's, and Periodic Acid–Schiff (PAS) stainings. At low magnification, the lesion appeared as a well-circumscribed nodulocystic lesion with a lobulated pattern (Figure 1E), located into the lower dermis. At the periphery, it presented a capsule consisting of dermal compressed fibrous tissue (Figure 1F). At higher magnification, we observed that the lobular proliferations were composed of basaloid cells at the periphery, transitional cells and ghost cells toward the center, and eosinophilic cornified material in the center of the lesion (Figure 2A). The basaloid cells did not exhibit distinct cell borders and were tightly packed. They had deeply basophilic nuclei and scant cytoplasm (Figure 2B). A discrete nuclear pleomorphism and typical and atypical mitoses were also observed (Figure 2C). Unlike these, the ghost cells showed distinct borders, were enucleated and with a central unstained area (Figure 2D). Between the previously shown two cells categories were present the transitional cells with a squamous cell morphology. Many of the lobular structures displayed little or even absent basaloid cells, most of their volume being occupied by keratinized ghost cells. In the ghost cell regions we observed many calcifications (Figure 2E), as well as foreign body granulomas with multinucleated giant cells as a response to the presence of such cells (Figure 2F). The latter were more common in regions where keratinized debris was abundant.

### Immunohistochemical findings

Serial sections obtained during the histopathological investigation were processed by immunohistochemistry using a series of antibodies listed in the table below (Table 1), and as a visualizing system the Bond Polymer Refine Detection kit (Leica Biosystems, DS9800) and Novolink Polymer Detection Systems (Leica Biosystems, RE7150), and the 3,3'-Diaminobenzidine (DAB) chromogen respectively, following the working instructions of the manufacturer. Analyzing the data, we have noted the existence of a similar immunoprofile to that of the outer

root sheath of the normal hair follicle (CK5+/CD10+/CD138+/β-catenin+/p63+/DOG1+/S100+) (Figure 3, A–F). For the β-catenin marker, the reactivity was noticed in all pilomatricoma (PM) cellular compartments with basaloid cells as the most reactive, followed by the transitional cells, respective the ghost cells. The first two tumoral cell types exhibited reactivity in all cellular compartments (membrane, cytoplasmic and nuclear), while for the ghost cells the reactivity was confined only at the membrane. The immunohistochemical investigation in terms of tumorigenesis revealed the involvement of some regulatory proteins of the cell cycle (COX2, cyclin D1, p16, p53, galectin 3) (Figure 4, A–D and F) and of the main proteins that regulate apoptosis (Bcl-2, Bcl-6, galectin 3) (Figure 4, E and F).

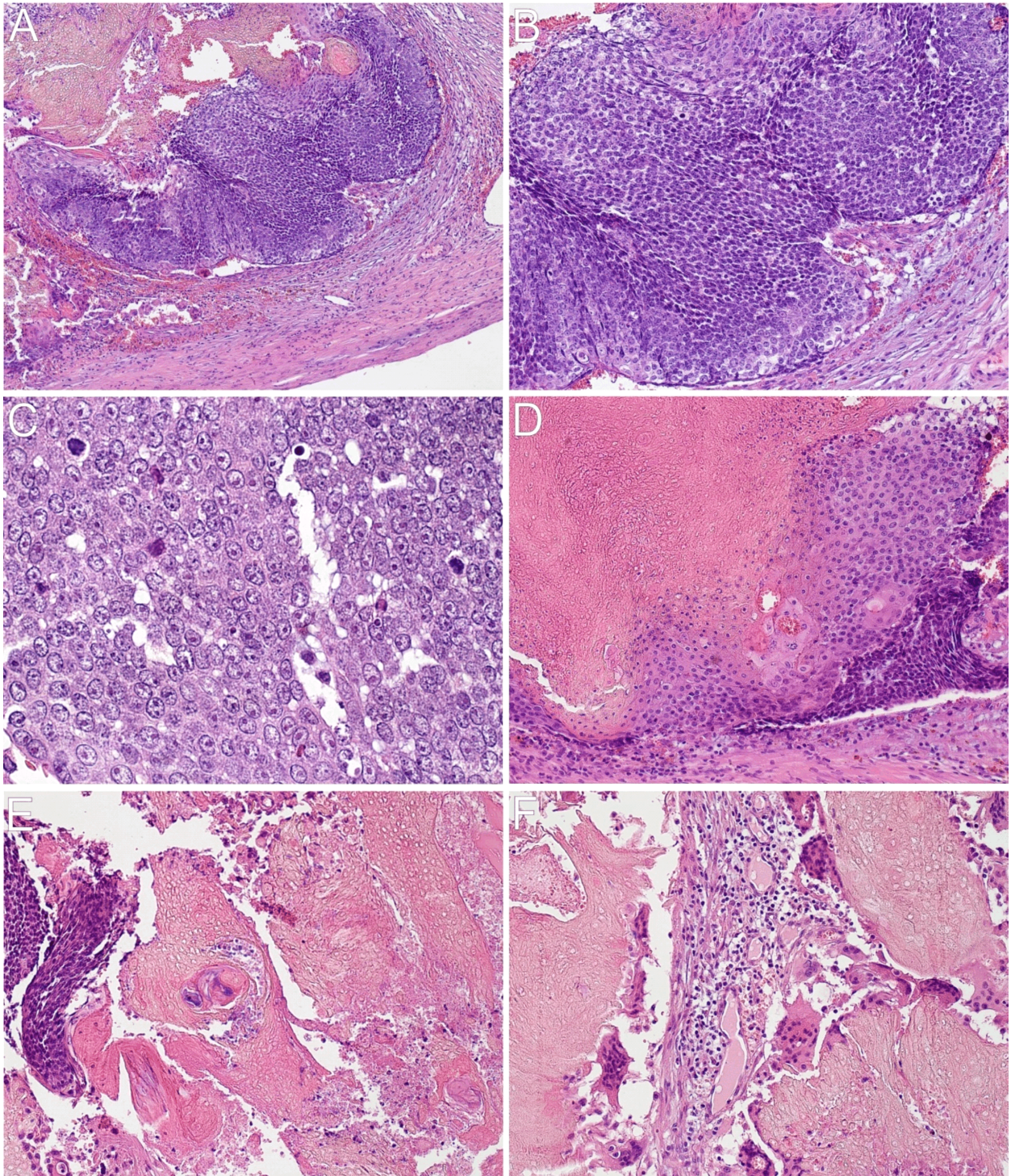
**Table 1 – List of the primary used antibodies and their reactivity in the tumoral pilomatricoma cells**

Antibody	Clone/ Manufacturer	Reactivity pattern		
		Basaloid cells	Transitional cells	Ghost cells
CK5	XM26/L.B.	+++ C/M	+ C	± C
CK8/18	5D3/L.B.	++/+ C/M	–	–
CK20	PW31/L.B.	–	–	–
CD10	56C6/L.B.	++/+ C/M, more prevalent at the periphery	± C	± C
p63	7JUL/L.B.	+++ N	–	–
CD138	MI15/L.B.	–/± C/M	++/+ C/M	–
β-Catenin	17C2/L.B.	+++ C/M/N	++ C/M/N	+ M
S100	Z0311/Dako	–	++ C/N	–
Melan A	A103/L.B.	–	–	–
Calretinin	CAL6/L.B.	–	–	–
CD117*	T595/L.B.	–	–	–
DOG1	K9/L.B.	–	++/+ M	–
WT1	WT49/L.B.	–	–	–
COX2	4H12/L.B.	++/+ C	+++ C	–
Cyclin D1	P2D11F11/ L.B.	++ N, at the periphery	+/- N	–
p16	CINtec® p16 kit/Roche	++ C/N	± C	–
p53	DO7/Dako	+++ N	± N	–
Bcl-2	bcl-2/100/D5/ L.B.	+++ C/M	–	–
Bcl-6	LN22/L.B.	–	+++ N	–
Galectin 3	25C1/L.B.	–	+++ C/M/N	–

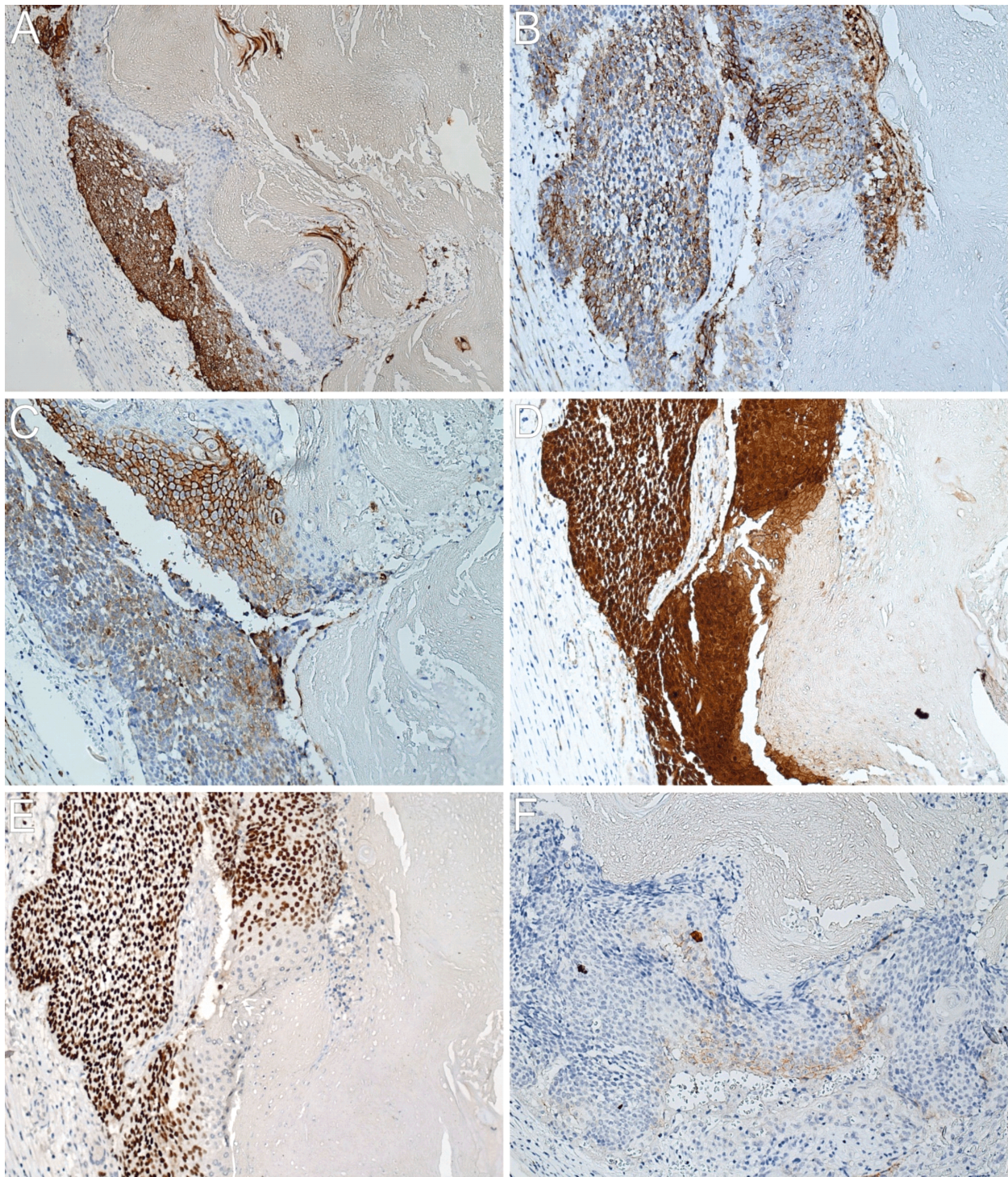
CK: Cytokeratin; CD: Cluster of differentiation; DOG1: Discovered on gastrointestinal stromal tumors (GIST) 1; WT1: Wilms tumor 1; COX2: Cyclooxygenase 2; Bcl: B-cell lymphoma; L.B.: Leica Biosystems; C: Cytoplasmic; M: Membranar; N: Nuclear; +++: Intense reactivity; ++: Moderate reactivity; +: Weak reactivity; –: Absence of reactivity; \*: Cytoplasmic intense reactivity in the stromal mast cells.

## Post-operative management

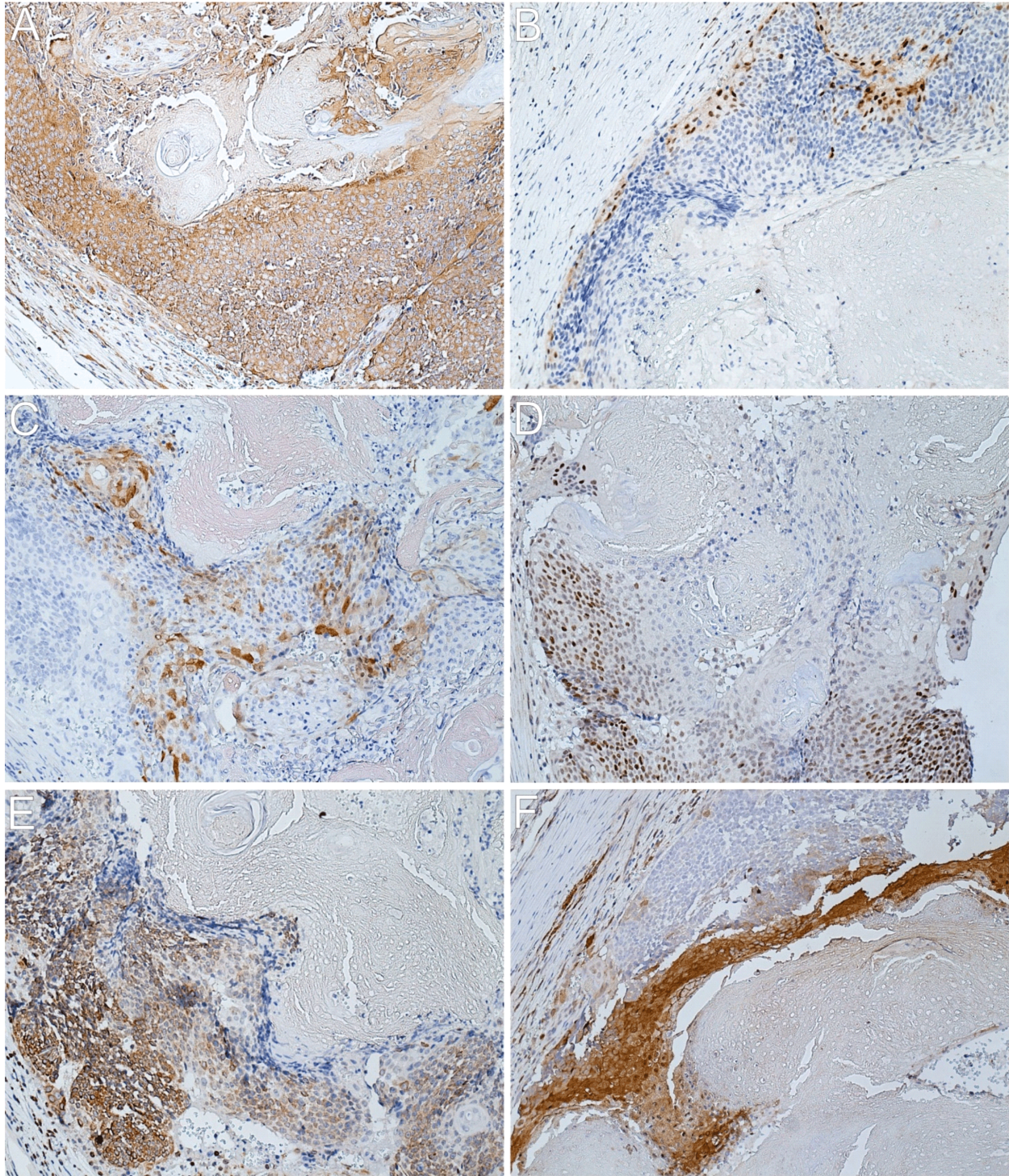
A final diagnosis of right preauricular skin pilomatricoma was established. The patient was discharged as cured from the surgical point of view and did not present any recurrence within a period of eight months of follow-up.



**Figure 2 – (A) Neoplastic lobule composed of basaloid cells at the periphery, transitional cells and ghost cells toward the center; (B) Basaloid cells without distinct cell borders, tightly packed, with deeply basophilic nuclei and scant cytoplasm; (C) Basaloid cells showed discrete nuclear pleomorphism and typical and atypical mitoses; (D) Ghost cells presented distinct borders, were enucleated and with a central unstained area; (E) Ghost cell regions with calcifications; (F) Multinucleated giant cells at the periphery of ghost cell regions. HE staining: (A)  $\times 100$ ; (B, D–F)  $\times 200$ ; (C)  $\times 630$ .**



**Figure 3 – Immunohistochemistry, DAB staining (brown), ×200:** (A) Cytoplasmic and membrane reactivity for CK5 more obvious in the basaloid neoplastic cells; (B) Cytoplasmic and membrane reactivity for CD10 more obvious in the basaloid neoplastic cells from tumor periphery; (C) Cytoplasmic and membrane reactivity for CD138 more obvious in the transitional neoplastic cells; (D) Cytoplasmic, membrane and even nuclear reactivity for  $\beta$ -catenin in the basaloid neoplastic cells; (E) Nuclear reactivity for p63 in the basaloid neoplastic cells; (F) Membrane reactivity for DOG1 in the transitional neoplastic cells. DAB: 3,3'-Diaminobenzidine; CK: Cytokeratin; CD: Cluster of differentiation; DOG1: Discovered on gastrointestinal stromal tumors (GIST) 1.



**Figure 4 – Immunohistochemistry, DAB staining (brown), ×200: (A) Cytoplasmic reactivity for COX2 in the basaloid and transitional neoplastic cells; (B) Nuclear reactivity for cyclin D1 more obvious in the basaloid neoplastic cells from tumor periphery; (C) Cytoplasmic and nuclear reactivity for p16 more obvious in the basaloid neoplastic cells; (D) Nuclear reactivity for p53 more obvious in the basaloid neoplastic cells; (E) Nuclear reactivity for Bcl-2 in the transitional neoplastic cells; (F) Cytoplasmic, membrane and even nuclear reactivity for galectin 3 in the transitional neoplastic cells. DAB: 3,3'-Diaminobenzidine; COX2: Cyclooxygenase 2; Bcl-2: B-cell lymphoma-2.**

## Discussions

The origin of this skin tumor was proved to be in epidermal basal layer from the residing stem cells that could differentiate as hair matrix cells [14], thus currently is considered to be a benign skin appendage neoplasm tumor of the hair follicle. Its etiology is not fully understood, in some cases a history of trauma, insect bites, surgery [4] and even vaccines [15] being documented. In most isolated PMs are found either a mutation in the adenomatous polyposis coli (*APC*) gene or a mutation in the catenin beta 1 (*CTNNB1*) gene, responsible for encoding  $\beta$ -catenin, with direct impact on tumorigenesis via the Wnt- $\beta$ -catenin-transcription factor (TCF)-lymphoid enhancer binding factor (LEF) signaling pathway [16, 17]. Also, in such tumors, an over expression of bcl-2 proto-oncogene was documented, proving to suppress the tumoral cell apoptosis and thus contributing to its pathogenesis [18]. On the other hand, PCs may be associated with many genetic disorders, such as Turner syndrome, myotonic dystrophy, Rubinstein-Taybi syndrome, trisomy 9, Soto syndrome, Gardner syndrome, 21-hydroxylase deficiency, trisomy 9, trisomy 18, myosin heavy chains (*MYH*)-associated polyposis, celiac disease, and *xeroderma pigmentosum* [19–22]. Besides these, some data pointed out the possible association of this tumor with chronic diseases, sarcoidosis, angiomyxoma and hypercalcemia and increased levels of the parathyroid hormone-related protein [23–25]. In addition, in the literature were quoted PM cases with familial aggregation [26].

Its true incidence in the general population is unknown, different published case series reporting values ranging between 0.001% to 0.0031% from all dermatological histology specimens [27, 28] or an incidence about 1.04% of all benign skin tumors [4]. Most authors designate PS as the second most common skin tumor after melanocytic tumors, the most common benign skin tumor in pediatric patients and accounting for 20% of skin appendages tumors in most casuistries [29–32]. In our experience, the presented case is the first one reported in the last 30 years in the Department of Oral and Maxillofacial Surgery.

Our case largely corresponded to the epidemiological profile of such tumors. Most of the reported case series indicate that there is a bimodal peak distribution for this skin appendage tumor, with the highest incidence during the first and second decades of life and with a second lower peak between 50 and 65 years of age [4, 9, 25, 33, 34]. The literature data specifies that at least 40% of the cases occur before the age of 10 years [4, 34, 35] and about 20–30% develops after 50 years old [9, 12, 33]. It seems that PMs are more common in women, with a female to male ratio ranging between 0.43:1 to 2.45:1 [9, 25, 31, 34, 36]. This type of tumor has the propensity to develop in the head and neck regions with the head as the most frequently affected [4, 12, 34, 35]. In the latter location, the most common involved sub-sites in decreasing order were the cheek, periorbital and periauricular areas. Although usually the PMs manifest as solitary lesions, some authors reported multiple tumors in the same

individual with an incidence ranging between 2–10% of reported cases [4, 12, 34, 35].

Clinically, our case was initially diagnosed as sebaceous cyst or parotid tumor. According to the data from the literature, the accuracy of the clinical diagnosis for this entity can varies between 28.9% [31] and 46% [37]. As an explanation for this, the authors had incriminated the lack of clinical specific features. However, highlighting of some clinical features, such as: (i) a firm, mobile, non-tender, slow growing tumoral mass, (ii) blue-red discoloration of the overlying skin, (iii) multifaceted, angulated appearance of the overlying skin – “tent sign” [38], and (iv) “teeter-totter” sign, we can increase the chance of a right diagnosis [34, 39]. In the same way, we must keep in mind also the need for differential diagnosis with other clinical entities, such as dermal and subcutaneous masses (sebaceous cysts, epidermoid cysts, brachial remnants, dermoid cysts, adenopathies, degenerating fibroxanthoma, basal cell carcinomas and neurofibromas), calcified lesions (calcified epidermoid cyst, chondroma, calcinosis cutis, osteoma cutis, foreign body reactions or ossifying hematomas) and, in the case of preauricular lesions, must be included the primary and secondary parotid gland tumor lesions, preauricular sinuses, and sialadenitis of the parotid gland [12, 34, 35].

In our case, the ultrasound imaging revealed a well-defined, hyperechoic nodule with multiple calcifications. The literature data states a minor role of the imaging methods in the diagnosis of such tumors. The ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and plain soft-tissue radiography may be useful in the differential diagnosis of PMs by identifying calcifications, ruling out a vascular or lymphatic tumor and in the preauricular lesion may exclude the parotid tumors [35, 40].

The key role in the diagnosis of this tumor type is held by the histopathology exam. Typically, the PM have a lobulated pattern with basaloid cells at the periphery, enucleated “ghost” cells in the center and transitional cells between the aforementioned cell populations [12]. As we described, commonly could be reported areas of calcification within the shadow cell regions and infiltration with multinucleated cells formed at sites of rupture. Without treatment or prognostic implication there have been described four distinct morphological stages, namely: (i) early small cystic lesions; (ii) large cystic lesions; (iii) early regressive lesions with foci of basaloid cells, shadow cells and infiltration with lymphocytes and multinucleated giant cells; and (iv) late regressive lesions with numerous shadow cells and absence of basaloid cells and inflammatory cells [41]. From this point of view, our case would fit in the early regressive stage. Moreover, in the literature are quoted histopathological variants such as: (i) bullous PM (that show dilated lymphatic vessels, lymphedema, dilated blood vessels and disruption of collagen fibers) [42]; (ii) pigmented PM (in which occur either an increased melanin deposition and/or a prominent hyperplasia of dendritic melanocytes within basaloid cell nests) [43]; (iii) proliferating PM (that are relatively large with many neoplastic lobes made up of basaloid cells, with frequent mitoses and nuclear atypia [44].

Our study has shown a tumor immunoprofile close to that of the outer root sheath of the normal hair follicle. Many studies proved the reactivity of basaloid cells and transitional cells from PMs to  $\beta$ -catenin with different subcellular patterns suggesting the involvement of this biomarker both in the cell–cell adhesion process as well as in the tumorigenesis by controlling the cellular proliferation and differentiation [16, 45, 46]. It seems that at least 75% of human PMs had  $\beta$ -catenin gene mutations [47] that lead to increased levels of free  $\beta$ -catenin both in the cytoplasm and nucleus, which in turn causes tumorigenesis [48]. At the same time, the  $\beta$ -catenin immunoreactivity similitude between PM and normal hair follicles suggests the origin of this benign skin tumor from the matrix cells of hair follicle [45, 49]. The hair matrix cell origin of PM is also supported by the studies that showed neoplastic cell reactivity to AE1/AE3 cytokeratin [50], CD138 cell adhesion protein [51, 52], CD10 zinc-dependent cell membrane metalloprotein [53], and other hair proteins [54]. This reactivity is gradually lost as the basaloid cells are transformed into ghost cells persisting in the latter only a weakly positive AE1/AE3 reactivity [50]. In this regard, it was hypothesized that the neoplastic basaloid cells of PM could undergo an “aberrant keratinization” [55] or more appropriate that they could suffer an apoptosis-like process [52] and the cytoplasmatic fibrillar structure found in ghost cells are not keratin filaments but rather tonofilaments of abnormal keratin, not yet well characterized [50]. On the other hand, in some cases with rapid growth there has been identified a cell compartment consisting of undifferentiated basophilic cells that showed c-KIT reactivity [56] and *p53* mutations and high proliferative activity [57], compartment which would be responsible for tumor progression and the development of giant tumors.

Primarily, the differential diagnoses for PM must include other neoplasms or tumor-like lesions with matrical differentiation, such as: matricoma (lacks the typical central cystic component and have small areas of shadow cell formation), matrical carcinoma (presence of cytological atypia, infiltrative border, transition to squamous cells, necrosis, mitotic figures, variable sarcomatoid features), melanocytic matricomas (presence of the same malignant features as those outlined in the previous entity), basal cell carcinomas with matrical differentiation (composed mainly by basaloid cells with scant cytoplasm and elongated hyperchromatic nuclei, and presenting peripheral palisading, peritumoral clefting and mucinous alteration of surrounding stroma), trichoepithelioma (composed of basaloid cells that often had bulbar differentiation and even achieving abortive hair follicles in a more dense and cellular stroma), trichofolliculoma (where the proliferating epithelium achieve small follicles that irradiate from a central larger follicle), trichilemmal cyst (in which the peripheral layer of basaloid cells shows a palisading pattern), proliferating trichilemmal cyst (consist of squamous epithelium bands with trichilemmal-type keratinization, occasionally with prominent atypia, and focal stromal invasion), and keratoacanthoma (where the proliferating epithelium accomplish

deep, large lobules of keratinized squamous cells with central crypts filled with keratin). As well could be included epidermal cyst (lined by a keratinized epithelium with distinct granular layer, and has no calcification), keratinizing squamous cell carcinoma (invasive malignant lesion with obvious squamous differentiation as intercellular bridges) and in the pre-auricular location, we should also take into consideration the salivary gland tumors composed of basaloid cells, such as pleomorphic adenoma, basal cell adenoma, basal cell adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinomas and small cell undifferentiated carcinoma.

Complications of pilomatricoma are rare, occasionally they could grow to giant size (designated as giant PMs, when they have more than 5 cm in diameter) leading to compression in the vicinity (for example in pre-auricular location could be responsible for facial nerve paralysis) [7, 10, 13, 24]. In some of these cases, the tumoral growth was fast, in less than a year displaying histological features that are suggestive to a possible malignant transformation [56]. This possible evolution is reported in less than 60 cases of PMs and usually takes place in older patients and after repeated recurrent tumor excision [4, 7, 58]. Histopathologically, in these cases it becomes obvious the nuclear and cellular pleomorphism, frequent and often atypical mitoses, necrosis, lymphovascular invasion and infiltration of the adjacent structures [4, 12, 31]. Recurrence rate ranges between 0% and 3% [12, 31] and most likely, this is due to inadequate surgical excision, and rarely is due to malignancy [4, 59, 60].

## Conclusions

The particularities of this case reside in age at which the tumor developed, its localization, presence of nuclear pleomorphism and typical and atypical mitosis, histopathological features of a late regressive lesion. Moreover, considering all these aspects, it becomes evident that for such lesions it is essential to make a differential diagnosis that must include a large variety of tumor and non-tumor lesions, booth of the skin and parotid gland.

## Conflict of interests

The authors declare no conflict of interests.

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**Corresponding author**

Marius Matei, Assistant Professor, MD, PhD, Department of Histology, University of Medicine and Pharmacy of Craiova, 2 Petru Rareș Street, 200349 Craiova, Dolj County, Romania; Phone +40723–535 854, e-mail: mariusmatei44@yahoo.com

*Received: February 22, 2018*

*Accepted: November 17, 2018*