The histopathological and immunohistochemical study of the local invasion in maxillary bone ameloblastoma

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INTRODUCTION

The ameloblastoma is among the less frequent odontogenic tumors and it is characterized by a general benign biological behaviour, with a high capacity of local invasion and a high risk for relapse. Still, it is a rare neoplasia, its global incidence being about 0.5 cases in a million inhabitants and per year. The morphological diversity of this type of tumor often leads to confusions, as a series of benign and malignant neoplasias, including cystic lesions, may histologically mime the ameloblastoma, giving a serious trial to the anatomopathologist. Although their behaviour is benign, the ameloblastoma has a local biological invasive behaviour, the tumor in its evolution causing the expansion of the maxillary bones, the thinning and erosion of the cortical bones and, subsequently, their invasion into the adjacent soft tissues.

Taking into consideration all these aspects, the present study proposed the epidemiological, histopathological, immunohistochemical and statistical study of 62 patients diagnosed with ameloblastomas over a period of 8 years, between 2008 and 2015. The epidemiological study highlighted the prevalence of maxillary ameloblastomas in women, in the 4th life decade, mainly affecting the premolar/molar area of the right mandible. The histopathological study highlighted the prevalence of solid forms of ameloblastoma, with the predominant follicular and plexiform subtypes. The bone invasion, as a sign of the aggression of these tumors was recorded by us in almost two thirds of the investigated cases, a morphological aspect more frequently present in the follicular solid subtype and in the plexiform solid one, respectively.

The immunohistochemical analysis mainly involved the particularities of the invasion process, of these tumors being investigated the following: the immunoreactivity for the Zinc-dependent CD10 metaloproteinase, the chemokine receptor CXCR4, the growth factor EGFR, the Podoplanin transmembrane sialomucin, the N cadherin adhesion molecule, the transcriptional Snail factor, the F-actin microfilaments and WASL protein – regulatory for the reorganization of the actin cytoskeleton. Thus, it was proven the involvement of the F-actin, WASL, Snail, podoplanina and EGFR markers, for which, independent of the histopathological subtype, there were obtained the highest scores of immunoreactivity. At the basis of the ameloblastomas local aggressiveness, there were: an active process of an epithelial-
mesenchymal transition (proven by the implication of the Snail transcription factor, of podoplanin and ivadopodic protein WASL that coordinates the intracellular rearrangement of the F-actin filaments) and the subexpression of the growth factor EGFR (involved in the tumor progression and growth). This study highlights the certain involvement of some of the biomarkers investigated in the local aggressive behaviour (Snail, Podoplanin, EGFR and CXCR4), underlying their prognosis value, and also their therapeutical use, these being considered as efficient molecular targets in the treatment of these odontogenic tumors.

**Key words:** ameloblastoma, prognosis factors, immunohistochemistry, local invasion, odontogenic tumor

**CHAPTER I. EPIDEMIOLOGY OF ODONTOGENIC TUMORS** – presents the latest data on the incidence, geographical distribution, age, sex distribution and topographic localization of these neoplasias.

**CAPITOLUL II. ETIOPATHOGENY OF ODONTOGENIC BENIGN TUMORS** – at first there are described the main ways of molecular signaling ways involved in the etiopathogenesis of odontogenic benign tumors, from the perspective of the latest findings reported in the literature. Then, there is performed a review of the pathogenic ways involved in the tumorigenesis of maxillary ameloblastomas.

**CHAPTER III. PROGNOSIS FACTORS OF ODONTOGENIC BENIGN TUMORS INVASION, WITH A SPECIAL REFERENCE TO THE AMELOBLASTOMA** – here there is performed a review of the main types of benign odontogenic tumors with a local invasive potential, followed by a presentation of the biomarkers and molecular mechanisms at the basis of local aggression in ameloblastomas.

**STUDY OBJECTIVES**

I. Evaluation of the epidemiological and histopathological characteristics of maxillary ameloblastomas from the prognosis point of view, for a period of 8 years, by quantifying the following parameters:
   - epidemiological: sex, age of patients and tumor localization;
   - histopathological: the histopathological variant, type of cytological differentiations, type of tumor growth pattern, particular aspects of the stroma, presence/absence of invasion, morphological type of invasion.

II. Establishing the local aggressive immunoprofile of these tumors by investigating:
   - the biomarkers directly addressed to tumor invasion: CD10, CXCR4 and EGFR;
   - the biomarkers involved in the process of epithelial-mesenchyme transition of tumor cells: Podoplanin, N caderin, Snail, F-actin and WASL.
CHAPTER IV- HISTOPATHOLOGICAL STUDY OF AMELOBLASTOMAS.

RESEARCH MATERIAL – based on the cases from the Pathological Anatomy Laboratory of ”Professor MD PhD Dan Theodorescu” Oral and Maxillofacial Surgery Clinical Hospital Bucharest, represented by the archived paraffinum blocks. The study extended over a period of 8 years, the cases being selected between 2008 and 2015, including 62 cases of maxillary ameloblastoma that constituted the object of the histopathological study.

USED METHODS
The histopathological study was performed on the permanent samples processed in the classical histopathological technique of formalin fixation, paraffinum inclusion, microtome sectioning and Hematoxylin-Eosine (HE), Periodic Acid Schiff (PAS) and tricromic Van Gieson (tr. VG) stainings.

The studied variables were:
- Epidemiological ones: age, sex, environment, heredocolateral history (family history of ameloblastoma), personal medical history, subjective complaints that determined the patients to present to the doctor and disease history.
- Histopathological ones: the histopathological type and subtype of the investigated tumors, the tumor growth pattern, the cytological differences of the examined tumors, the tumoral stroma aspect, the invasion aspect and tumor growth.

RESULTS AND DISCUSSION
The sex distribution of our cases showed a slight prevalence of the ameloblastoma cases in women (51.60%), with no significant statistical differences regarding the sex distribution according to the histopathological subtype. The literature data indicated a uniform distribution of the cases regarding the two sexes [Dhanuthai et al., 2012] or a slight prevalence in men [Dias et al., 2013; Filizzola et al., 2014]. Regarding the age group distribution of the cases, we observed a large number of cases diagnosed from the 2nd to the 4th life decades. The mean value of the age at which ameloblastomas developed was 33 years old, being around 29 years old for the follicular subtype, 32 years old for the plexiform subtype and 53 years old, respectively, for the acantomatous one. Data in the literature, namely within the highest series of 3677 cases of ameloblastoma, reported that the patients’ age varied between 4 and 92 years old [Reichart et al., 1995]. The youngest patient reported with ameloblastoma was 2 years old [Fulco et al., 2010], while the oldest was 93 years old [Ord et al., 2002]. The most frequent localization of ameloblastomas in our cases was the premolar/ molar region of the mandible, namely 55% of all lesions localized at this level. About 56.45% of the tumors with this localization affected the right mandible. Most studies indicated the mandible as the most frequently interested part in comparison to the maxilla, with a ratio varying from 5:1 to 90:1 [Filizzola et al., 2014; Gardner et al., 2005]. There are geographical variations, in Asia being reported a ratio between 8:1 to 13.3:1 in comparison to North America, where this ratio varied between 3:1 and 6:1 [Dhanuthai et al., 2012].

In our study, the histopathological analysis of the surgical exeresis pieces highlighted the prevalence of solid forms of ameloblastoma with a percentage of 90.5%,
on the opposite side being peripheral ameloblastomas with a percentage of 3.15%. As far as solid ameloblastomas are concerned, the most frequent were by far the follicular ones, representing 74.2% of all cases, followed by the plexiform variant with 74.2% of all studied cases. In the group of follicular solid ameloblastomas, the best represented variant was the one diagnosed in 51.6% of all cases. In our study, the association of various growth patterns was observed in 23.5% of the investigated cases and consisted in the association between the follicular pattern with the plexiform and trabecular patterns. According to the literature data, solid ameloblastomas affect the mandible [Adeline et al., 2008; Ledesma-Montes et al., 2007], especially its posterior region [Adeline et al., 2008; Ledesma-Montes et al., 2007], the ratio of this variety of ameloblastoma incidence in the two gnatic bones being of 1:5.4 [Reichart et al., 1995].

Strictly from the histopathological point of view, the data regarding the incidence of various solid/ multicystic ameloblastoma subtypes are extremely variable. Thus, of 116 cases of ameloblastomas, Waldron and El-Mofty reported an incidence of 64.9% of the follicular type solid ameloblastoma, 16.9% of the plexiform subtype and an association between the two variants in 12.9% of all the investigated cases [Waldron & El-Mofty, 1987]. Still, Reichart et al., in the highest series of ameloblastomas reported in the literature (3677 cases) found an incidence of 35.4% for the follicular subtype, for the plexiform type a frequency of 31.5%, and for the ameloblastom variant an incidence of 11.8% [Reichart et al., 1995]. At the same time, the literature data indicate an incidence of 4.5% for the hybrid subtype of ameloblastomas [Waldron & El-Mofty, 1987].

**Bone invasion** was highlighted by us in 72.6% of all the investigated tumors, most often in the follicular subvariants (87.5% of the cases) and in the plexiform one (in all the investigated cases), having an aspect of large front invasion, with the thinning and erosion of the maxillary cortical faces. The literature data indicate ameloblastoma as a slow growing tumor that causes the bone cortical expansion, lingual and/or bucal faces penetration, and infiltration of the adjacent soft tissues, especially in the posterior localization of the mandible [Laskin et al., 2002]. Radiological studies identified the erosion of the maxillary cortical bone in over 80% of cases, and soft tissue infiltration in 87% of the cases, 37.5% of the patients being diagnosed with the follicular subtype of ameloblastoma [Fregnani et al., 2010].

**CHAPTER V. IMMUNOHISTOCHEMICAL STUDY OF AMELOBLASTOMAS.**

RESEARCH MATERIAL – was represented by a number of 20 ameloblastoma cases representative for the 62 cases that were histopathologically investigated. The average age of these patients was 41 years old, represented mainly by female patients (M:F=9:11) and were most frequently developed in the posterior region of the mandibular branch (17 cases). Regarding the presence of bone invasion, this was present in 11 cases, while regarding the histopathological subtype, there were 6 cases of follicular type, 2 cases of plexiform type, 1 acantomatous type, 1 cystic degenerescence type and 1 with granular cells.
MATERIAL AND METHODS

The immunohistochemical study was the the enzyme detection type, using the technique of MACH 4 MICRO-POLYMER-HRP (Biocare Medical; M4U534). The result of these immunohistochemical reactions consists in the visualization of the antigens investigated with the DAB chromogene, through their brown staining. For the study of the epithelial-mesenchyme transition, and of the expression of N-cadherin marker and the Snail transcription nuclear factor, respectively, we used double immunohistochemical reactions.

In the immunohistochemical study of the 20 ameloblastoma cases, we used the concentrated antibodies grown in rats or rabbits directed against humans, whose main characteristics are given in the table below:

| Table V.2 Antibodies used in the immunohistochemical study of ameloblastomas |
|----|----|----|----|
| Used antibody | Clone, Manufacturer | Dilution | Antigenic demasking |
| CD10 | Rat, Monoclonal, 56C6, Dako Cytomation | 1:50 | 0.1 M cytrate, pH 6 | Lymph ganglion |
| CXCR4 | Rabbit, Polyclonal, Thermo scientific | 1:500 | 0.1 M cytrate, pH 6 | Squamous carcinomas |
| EGFR | Rabbit, Polyclonal, Leica Biosystems | 1:50 | 0.1 M cytrate, pH 6 | Squamous carcinomas |
| Podoplanin | Rat, Monoclonal D2-40, Dako | 1:100 | 0.1 M cytrate, pH 6 | Lymph ganglion |
| N cadherin | Rat, Monoclonal 6G11, Dako Cytomation | 1:30 | 0.1 M cytrate, pH 6 | Pancreatic carcinoma |
| Snail | Rabbit, Polyclonal, Abcam | 1:50 | 0.1 M cytrate, pH 6 | Breast carcinoma |
| F Actin | Rat, Monoclonal, LifeSpan Biosciences | 1:50 | 0.1 M cytrate, pH 6 | Prostate |
| WASL | Rabbit, Polyclonal, Sigma-Aldrich | 1:75 | 0.1 M cytrate, pH 6 | Colon |

RESULTS AND DISCUSSION

By investigating the CD10 immunoreactivity in our cases, we observed the highest immunoreactivity in the variant with granular cells, both in the epithelium and the stroma, and, ultimately, in the peripheral variant. For all the investigated variants, the invasive forms presented the highest scores, the tumoral epithelium being highly reactive, in comparison to the stroma. Regarding the tumoral epithelium reactivity, we observed its presence only in the cytoplasm of the stellate reticle cells and not in the ameloblast-like peripheral cells. The maximum of reactivity was observed in the areas with squamous metaplasia and in the granular tumoral cells, respectively, with a membranary and cytoplasmatic pattern. A series of authors showed the membranary and cytoplasmatic immunopositivity for CD10 of the neoplastic cells in the ameloblastomas [Masloub et al., 2011], the reactivity being higher in the infiltrative areas of odontogenic epithelium [Iezzi et al., 2008]. Also, there was shown that the CD10 expression was higher in the various forms of multi cystic ameloblastoma, in comparison to the
unicystic ameloblastoma, a fact that may explain the extremely aggressive behaviour of the solid ameloblastoma in comparison to the unicystic one [Masloub et al., 2011]. On the other side, Iezzi et al. showed that those cases of solid ameloblastoma presenting a high risk for relapse were associated to a higher rate of CD10 expression in the peritumoral stromal cells [Iezzi et al., 2008]. The authors suggested that the CD10 expression in the stromal cells of the solid ameloblastoma is associated with the local tumoral invasion in these cases, and that this immunoreactivity could be useful in identifying the areas with an aggressive potential, even in the ameloblastomas with a low risk.

CXCR4 was used by us for the first time for the study of the various variants of ameloblastomas. Thus, the maximum of reactivity was observed in the invasive acamamous and luminal unicystic forms, at the opposite side being observed the non-invasive typical follicular variant and the one with granular cells. On the whole, the cells of the stellate reticle were more reactive in comparison to the ameloblast-like peripheral cells, and the reaction pattern was a different one, namely a cytoplasmatic one for the cells of the stellate and membranary reticle for peripheral cells. Also, we observed an increase of the reactivity, especially towards the invasion front. Strictly connected to the expression of this marker in the dental tissues, there was proven only a poor reactivity in the normal dental pulp tissue and a high expression in the inflamed pulp tissue, suggesting a possible recruiting of the pulp cells CXCR4- positive towards the inflammation site [Jiang et al., 2008].

In our study, the maximum of reactivity for EGFR was observed in the unicystic and peripheral variant, followed by the follicular and plexiform ones. The reactivity for EGFR, independent of the histopathological subtype, was higher at the periphery of the tumoral proliferations and in the invasion front, the dominant pattern being a cytoplasmatic one. Also, the peripheral ameloblast-like cells were much more reactive and with a mainly membranary pattern, while the cells of the stellate reticle were less reactive and with a mainly cytoplasmatic pattern. Thus, if Shrestha et al. did not find any immunoreactivity in none of the 23 examined solid ameloblastomas [Shrestha et al., 1992]. Vered et al. [Vered et al., 2003], Abdel-Aziz and Amin [Abdel-Aziz & Amin, 2012] and Li et al. [Li et al., 1993], respectively, observed its expression in all the studied cases. The maximum of the intensity seems to be in the follicular and squamous differentiation forms, the peripheral row of ameloblastic-like neoplastic cells being more reactive in comparison to the stellate reticle cells, this thing being highlighted especially in the cases of bone and extra bone invasion [Oikawa et al., 2013; Ueno et al., 1994].

In our study, the reactivity to Podoplanin was maximum in the cases of unicystic and invasive plexiform ameloblastoma, closely followed by the cases of invasive follicular ameloblastoma, the follicular granular cell case and the peripheral ameloblastoma case, respectively. Independent of the subtype and invasion, the reactivity was present especially in the ameloblast-like peripheral cells with a main membranary pattern. An increase of reactivity was signaled especially at the periphery of the tumoral proliferations and especially in the invasion front, this increase being recorded especially in the cytoplasm, both in the peripheral cells and the ones of the stellate reticle. A series of studies showed that, in the benign odontogenic tumors, Podoplanin was expressed especially by the cells at the periphery of the tumoral proliferations, cells
that are supposed to be responsible for the local invasion of this tumor [Caetano et al., 2013; Zustin et al., 2010; Friedrich et al., 2012; González-Alva et al., 2011; Tsuneki et al., 2012]. Strictly at the level of follicular ameloblastomas, the cytoplasmatic and membranary expression of Podoplanin was observed especially in the column peripheral cells of the tumoral islands, and, usually, the stellate reticle cells of the islands center were not immunoreactive [Caetano et al., 2013; Tjioe et al., 2012; Siar et al., 2015]. At the same time, the maximum of Podoplanin reactivity was observed in the invasion areas and in the tumoral areas, respectively, with the highest proliferative activity [Ganvir et al., 2016].

Our investigation highlighted a maximum of reactivity for N-cadherin in the case of luminal unicystic and invasive plexiform ameloblastomas, closely followed by the invasive follicular variant. Independent of the histopathological subtype and the local behaviour, the maximum of reactivity was identified in the ameloblast-like cells, with a main membranary pattern. In the invasion front, the reactivity was higher, the reaction pattern being a nuclear one in the peripheral cells, and, also, the reaction becomes visible in the stellate reticle cells. In the only study that investigated the N-cadherin expression in ameloblastomas, there was reported a rate of its expression in 87.5% of the investigated cases, with a membranary localization of the signal, especially in the ameloblast-like peripheral column cells [Kusafuka et al., 2011]. Reported to subtypes, the authors found that about 61.9% of the follicular ameloblastoma cases were reactive and that 61.5% of the plexiform ameloblastoma cases were positive for this marker.

In our study, a maximum of reactivity for Snail was recorded in the cases of invasive follicular ameloblastomas, followed by the case of unicystic ameloblastoma and the one with invasive cystic degenerescence. The expression of this marker was more obvious in the invasive forms, independent of the histopathological subtype, and the ameloblast-like peripheral cells were the most reactive, with a main cytoplasmatic and membranary pattern. In the invasion front, the reactivity was also present in the stellate reticle cells and, moreover, we also observed a nuclear and/ or cytoplasmatic colocalization of this marker with N-cadherin, especially in the follicular, plexiform and unicystic forms. Siar and Ng showed that the Snail factor is expressed in 94% of ameloblastomas, being better expressed in comparison to the other transcriptional factors involved in EMT (Slug, SIP1 and Twist) [Siar & Ng, 2014]. The authors did not find any significant differences regarding the Snail expression, according to the tumor topography (center versus invasion front) or the architectural pattern (solid ameloblastom versus unicystic one). Still, the immunoreactivity for this marker proved to be higher in the ameloblast-like peripheral cells, in comparison to the ones in the stellate reticle.

In our study, the most immunoreactive for F-actin proved to be the invasive ameloblastoma forms, namely the follicular, acanatomatous, granular cell and unicystic, luminal variants. Independent of the histopathological subtype, the peripheral ameloblast-like cells were more reactive, with a main cytoplasmatic and membranary pattern. Moreover, in the invasive forms, at the invasive front the reactivity was more intense, being observed in the peripheral cells and at nuclear level. In our study, somehow similar to the F-actin immunoreactivity, WASL was better expressed by the invasive ameloblastoma forms, with a maximum of reactivity in the follicular granular cell ameloblastoma, the unicystic luminal ameloblastoma and in the cases of invasive follicular and plexiform ameloblastoma. Their reactivity was a lot higher at the invasion
front. Moreover, both for WASL and for F-actin, in the invasive forms, especially at the invasive front, we observed an intense reactivity of the stromal fibroblasts. Siar et. al. examined the expression of the invadopodia proteins (cortactin, N-WASP, WIP) and F-actin in 87 ameloblastomas, showing their subexpression (cortactin in 83.9%; N-WASP in 67.8%; WIP in 88.5% and F-actin in 100% of the investigated cases) [Siar et al., 2016]. Cortactin was more intensely expressed in the tumoral epithelium than in the stroma, while WIP and F-actin were present especially in the invasion front. The authors concluded that, at least in part, the process of local invasion of ameloblastomas is dependent on the intra cellular distribution of invadopodia proteins in relation to the cytoskeletal dynamics of the F-actin filaments [Siar et al., 2016].

CHAPTER V - FINAL CONCLUSIONS

▪ Between 2008-2015, ameloblastomas represented about 26.5% of the total of operated odontogenic tumors, alongside with the odontomas, being one of the most frequent odontogenic neoplasia of our cases.

▪ The study of sex distribution indicated a mild prevalence of the cases in women, with a sex ratio of 1.1 in its favour, with no significant statistical differences in relation to the histopathological subtype. The case distribution on age groups showed a large age area, this type of odontogenic tumor being developed between the 2nd and 9th life decade. The study of lesion topography indicated the main localization of ameloblastomas in the premolar/ molar region of the right mandible (55%).

▪ The histopathological study recorded the prevalence of solid forms of ameloblastoma by a percentage of 90.5%, at the opposite side being the peripheral ameloblastomas, by a percentage of 3.15%. Regarding the solid ameloblastomas, the most frequent, by far, were the follicular ones (74.2%), and, on the second place, there situated the plexiform variant (74.2%).

▪ The rarest variant diagnosed by us was the peripheral ameloblastoma, namely in 2 cases (3.22%), while the unicystic ameloblastoma variant was diagnosed in 6.45% of the cases. In 23.5% of the investigated cases, we observed the association of various growth patterns, most frequently being related to the association of a follicular and trabecular plexiform pattern.

▪ The bone invasion was highlighted by us in 72.6% of the investigated cases, most frequently in the follicular subtype (87.5%) and in the solid plexiform one (100%), getting the aspect of ”pushing border”, with the thinning and erosion of the maxillary cortical planes;

▪ In the process of local invasion of the ameloblastoma, there seem to be involved especially the markers for: F-actin microfilaments, WASL protein (regulatory for the actin cytoskeleton reorganization), the Snail transcriptional factor (involved in the regulation of the epithelial-mesenchymal transition process), transmembrane sialomucin podoplanin (controlling the cellular mobility) and the growth factor EGFR involved in the local tumor progression and growth. For these two markers, independent of the histopathological subtype, there were obtained the highest scores of immunoreactivity;

▪ After the immunohistochemical investigations, there may be concluded that, at the basis of the ameloblastoma local aggressiveness, there existed, on the one side, an active epithelial-mesenchyme transition process (shown by the involvement of the Snail transcription factor, of podoplanin and of WASL invadopodia protein that coordinates
the intra cellular rearrangement of the F-actin filaments) and, on the other side, the subexpression of the EGFR growth factor (involved in the local tumor progression and growth);

- The most aggressive histopathological variants of ameloblastoma, according to the obtained immunoreactivity scores, seem to be the unicystic variant and the polycystic one, respectively, with the typical and plexiform follicular subtypes. An intermediary behaviour seems to have the acanthomatous variant and the granular cell ones, respectively, and the least aggressive seem to be the peripheral ameloblastomas and the cystic degenerescence ameloblastomas;

- The most aggressive tumoral behaviour, independent of the histopathological variant, seems to be the one of the ameloblast-like cells, at the periphery of the tumor proliferations and especially at the invasion front;

- In the local invasion process of ameloblastomas, there also interferes the stroma adjacent to the tumoral proliferations, a fact shown by the immunoreactivity existence at this level for the following markers: CD10, F-actin and WASL;

- This study highlights the certain involvement of some of the investigated biomarkers in the local aggressive behaviour (Snail, podoplanin, EGFR and CXCR4), thus underlying their prognosis value, and also their therapeutical utility, being prone to consitute efficient molecular targets in the treatment of these odontogene tumors.

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