Histopathology of Parotid Pleomorphic Adenomas: A “Pleomorphic Approach” to a Demanding Lesion

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Objectives/Hypothesis: The aim of this study was to identify potential associations between epidemiologic, morphologic, and histopathologic features in pleomorphic adenomas (PAs) of the parotid gland in order to extract information about the natural course and biologic behavior of these lesions on the basis of a single-center series of 845 cases within a period of 15 years.

Study Design: Retrospective study in a tertiary academic center.

Methods: For this study, an experienced head and neck pathologist critically re-evaluated the histological slides of the pathological specimens of all patients who underwent a parotidectomy for PA of the parotid gland between 2006 and 2020.

Results: A total of 845 cases made up our study sample. Our analysis showed a statistically significant association of the histologic subtype with younger age ($P = .001$) and maximal diameter ($P = .044$), with the hypocellular type being encountered more often in younger patients and in smaller lesions. The same subtype was significantly associated with an incomplete capsule ($P = .001$), pseudopodia ($P = .006$), and satellite nodules ($P = .001$). An incomplete capsule was associated with the presence of pseudopodia ($P = .001$) and satellite nodules ($P = .001$).

Conclusion: It seems that various histologic subtypes have different capsule-producing properties. Apparently, over the course of time, tumor material builds a finger-like projection still inside the capsule, separates itself from the parenchyma with fibrous tissue still remaining enclosed within the capsule (pseudopodium), slowly penetrates the capsule (incomplete capsule), and leaves the main lesion taking a part of the capsule with it (satellite nodules).

Key Words: Parotid gland, pleomorphic adenoma, capsule, pseudopodia, satellite nodules.

Laryngoscope, 132:73–77, 2022

INTRODUCTION

Among the benign lesions of the parotid gland, the most demanding one is undoubtedly the pleomorphic adenoma (PA). A cut-off pseudopodium, a left-behind satellite nodule, a capsular defect dissected with narrow margins, or an accidental opening of the fragile hypocellular subtype have all been held accountable for contributing to the pathomechanism of recurrence.1–3 The non-negligible risk of a hard-to-treat recurrence, associated with the aforementioned characteristics of its capsule, justifies the basic principles of avoiding capsular exposure and resection with broad margins in the surgical management of the PAs.4–6 However, little is known about the biological behavior of the PA over time or the clinical significance of its variable histopathologic characteristics.

The aim of this study was to search for potential associations between epidemiologic parameters, morphologic factors, and histopathologic features in PAs of the parotid gland in order to extract information concerning the natural course and biologic behavior of these demanding lesions on the basis of a single-center series of 845 cases within a period of 15 years.

MATERIALS AND METHODS

This study was performed at an academic tertiary referral center specialized in salivary gland diseases (Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen–Nuremberg, Erlangen, Germany). For this study, an experienced head and neck pathologist (A.A.) critically re-evaluated the histological slides of the pathological specimens of all patients who underwent a parotidectomy for PAs of the parotid gland between 2006 and 2020. Based on tumor size, the number of histological slides per tumor varied from one to more than 10.

Surgical modalities in the parotid gland were defined as follows: extracapsular dissection (ED) was considered to be the removal of a tumor with a cuff of parotid tissue without intending to expose the main trunk or the branches of the facial nerve. If the main trunk was deliberately exposed before tumor dissection and only parts of the superficial lobe were removed along with the tumor, the procedure was defined as partial superficial parotidectomy (PSP). Removal of all the parotid gland lateral to the facial nerve was defined as lateral

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Editor’s Note: This Manuscript was accepted for publication on June 24, 2021.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.29726
parotidectomy (LP), whereas extirpation of the entire glandular parenchyma with preservation of the facial nerve was referred to as complete parotidectomy (CP). Concerning the histopathological analysis, PAs were divided into three histological subtypes on the basis of the stroma-cell proportion, according to the classification of Seifert et al.: the classic “mixed” subtype with a stroma content of 30% to 50%, the stroma-rich (“hypocellular”) subtype with a stroma content of more than 50%, and the cellular subtype with a stroma content of 30% or less. Furthermore, we paid special attention to the specific characteristics of the capsule likely to be associated with possible recurrences, such as the presence of an incomplete tumor capsule (IC), pseudopodia (PS), or satellite nodules (SNs). For comparison with the relevant literature, we used the nomenclature proposed by Zbaeren and Stauffer: a complete capsule assumed complete encapsulation of the tumor tissue in an anatomically intact fibrous capsule. A pseudopodium represents a “re-encapsulated” secondary nodule separated only by a layer of capsular fibrous tissue from the main tumor mass but localized within the main tumor capsule. Based on the sectioning plan, PS may appear either as mushroom-like capsular protrusions or as distinct small nodules closely associated with the main tumor and separated from it only by the fibrous capsule, but no normal fatty or salivary tissue is seen between them. Finally, SNs are distinct tumor nodules near the main tumor but outside the main tumor capsule, separated from it by salivary or fatty tissue without any connection to the main tumor (Fig. 1).

Statistical analysis was performed using multiple linear regression to examine the association between the histologic subtype and several epidemiologic and histopathologic characteristics. Furthermore, we performed univariate analysis to assess the relationships between the histopathologic features by applying the $\chi^2$ test with 95% confidence intervals (CIs). The software SPSS version 21 for Windows (SPSS, Inc., Chicago, Illinois) was used for the analysis. A $P$-value of <.05 was considered statistically significant. The Institutional Review Board of the University Hospital of Erlangen approved this study.

**RESULTS**

A total of 845 cases made up our study sample (296 men, 549 women; male–female ratio: 1:1.86).

![Wholemount picture of a parotideal pleomorphic adenoma with typical capsular characteristics.](image_url)

**Table I.**

| Histologic Subtype | Mean Age (yr) | Maximal Diameter (mm) | Gender (n) (Male/Female) | Incomplete Capsule (%) | Pseudopodia (%) | Satellite Nodules |
|-------------------|--------------|-----------------------|--------------------------|------------------------|----------------|-----------------|
| Hypocellular      | 46.7 ± 15.6  | 23.8 ± 10.0           | 134/269                  | 108/403 (26.8)         | 197/403 (48.8) | 48/403 (11.9)   |
| Mixed             | 49.3 ± 5.6   | 25.6 ± 12.9           | 85/151                   | 26/236 (11)            | 97/236 (41.1)  | 14/236 (5.9)    |
| Cellular          | 52.6 ± 14.8  | 25.8 ± 12.6           | 77/129                   | 20/206 (9.7)           | 74/206 (35.9)  | 8/206 (3.9)     |
Their mean age was 48.8 years (range: 12–87 years). The PA was removed by ED in 577 cases (68.3%), PSP in 75 cases (8.9%), LP in 72 cases (8.5%), and CP in 121 cases (14.3%). Our analysis did not detect a statistically significant influence of the surgical modality on the incidence of IC ($P = .872$), PS ($P = .523$), and SN ($P = .630$). Our analysis showed a statistically significant association of the histologic subtype of the PAs with age ($P = .001$) and maximal diameter ($P = .044$), with the hypocellular type being encountered more often in younger patients and in smaller lesions. The same subtype was significantly associated with an IC ($P = .001$), a PS ($P = .006$), and an SN ($P = .001$). An IC was associated with the presence of a PS ($P = .001$), and an SN ($P = .001$). The latter histologic characteristics were highly correlated with each other ($P = .001$). An analytic demonstration of our results is provided in Tables I–III.

### DISCUSSION

The first question emerging in our study could be: “How is the subtype of PA determined?” Apparently, the traditional classification of the PAs into three categories serves the purpose of communication between clinicians, as the percentage of stroma in PAs is not an ordinal (i.e., hypocellular, mixed, or hypercellular), but rather a...
“continuous variable” (taking all possible values between 0% and 100%). In 1981, Toole et al. provided evidence that epithelial cells secrete all the stromal components (glycosaminoglycan, collagen, and hyaluronic acid), which accumulate in the intercellular space until they disrupt the epithelium and cause its conversion to stroma.10 Various proportions of stromal components produced by the original epithelial component of PAs lead to variations in the proportion of epithelium to stroma in different parts of the tumor and variations between tumors, that is, different histologic subtypes. We could assume that a genetic-driven, more intensive desmoplastic activity of the epithelial cells in a subgroup of PAs from the beginning of tumorigenesis could already lead to a more intensive production of stroma with the transformation of epithelial into mesenchymal cells and the potential creation of the hypocellular subtype.

A thorough review of the relevant literature reveals various findings concerning the traditionally accepted comparative increase in the risk of recurrence with hypocellular PAs. On the one hand, Zbaeren et al. studied 25 recurrent cases but did not find an increased recurrence among hypocellular types.14 On the other hand, the working group from Cologne consistently confirmed the association.12,13 Several findings from our analysis tend to support the latter: first, hypocellular PAs showed a statistically highly significant tendency to show all critical capsular features examined in our study (IC, PS, SN). Second, this subtype was significantly associated with a younger age at the time of first surgery for PA. For obvious reasons, the duration of follow-up is longer in younger patients and PAs in this age group simply have more time in which to recur. In this respect, it could be claimed that the surgeon’s desire to perform less invasive procedures in this age group may lead to narrow or insufficient resection margins and result in a higher risk of recurrence. However, a potential association between hypocellular type and higher recurrence risk due to age has been greeted skeptically: in a study of 229 consecutive patients over 25 years, Laccoureeye et al. did not find a statistical relationship between age and risk of recurrence.14 From a surgical point of view, experienced parotid surgeons state that hypocellular PAs commonly give the impression of more compressible lesions, which are consequently more fragile and easier to rupture intraoperatively. From a pathogenetic point of view, Toole claimed further that certain components of the stroma (e.g. hyaluronic acid) of the PA seem to affect the biologic behavior of the epithelial cells, encouraging cell migration and thus favoring clinical recurrence.10 The fluid consistency of the myxoid stroma could be another factor for the potential spread of epithelial cells through microscopic ruptures of the capsule of a PA.15

The aforementioned association between the hypocellular subtype of PAs and an IC (often described as a thin “pseudocapsule”)16 has been known for more than four decades. Naeim et al. found a rate of capsular defects that were more than two times higher in hypocellular cases compared to mixed lesions and almost four times higher than the rate of hypercellular lesions.17 In order to investigate this well-established association, we searched primarily for literature on the nature of the PA capsule. Nakayama et al. described a bi-layered structure of the adenoma capsule, consisting of an inner layer with myofibroblasts among collagen fibers and an outer layer with dendritic interstitial cells.18 Concerning the evolution of this capsule, one scenario was based on the hypothesis that the PA is not initially encapsulated. According to Cotran et al.19 and Evans,20 a thin pseudocapsule and later a thicker capsule is formed as connective tissue within the gland condenses around the expanding PA. However, this scenario can explain neither the differences in the capsular properties between different PA subtypes nor the frequently seen IC, specifically in hypocellular cases. This argumentation leads to the assumption of some grade of participation of the tumor material (epithelium, stroma) in the formation of the capsule. For this reason, a second scenario, proposed by Stennert et al., sets out exactly from the opposite hypothesis:16 the capsule already exists at the beginning of the development of the PA. Potentially more aggressive behavior of the tumor parenchyma toward the capsule, with a varying “subtype-dependent” ingrowth of tumor material in the capsule, leads to a thinning of the capsule with the creation of defects as the tumor expands in size.16 The significant association of the hypocellular subtype with younger age and smaller size points further to the potential role of the tumor parenchyma in the development of a specific capsular phenotype.

The highly significant association of an IC with PS and SN could explain one aspect of the biologic behavior of PAs. It seems that, over the course of time, tumor material builds a finger-like projection still inside the capsule, separates itself from the parenchyma with fibrous tissue still remaining enclosed within the capsule (PS), slowly penetrates the capsule of the PA, and leaves the main lesion taking a part of the capsule with it (SNs), leaving a capsular defect in the main lesion. Interestingly, 1/5 of the PAs with SNs had an IC compared with the cases without SNs, in which only less than 6% of the cases presented this critical variant. Another piece of interesting information derived from the observation that 80% of the PAs with SNs did not demonstrate any capsular defects. This points to a self-protecting mechanism of the tumor, which apparently tries to seal the capsular defect that gave rise to the SN. This model seems reasonable, but cannot explain the pathogenetic mechanism in cases with a still questionable primary multifocality of PAs and a “de novo” appearance of multiple primary nodules.21,22 For the sake of correctness, it should be mentioned that the retrospective nature of the data collection, as well as the variable number of histological slides per tumor (based on tumor size), should be regarded as potential limitations of the present study.

CONCLUSION

Our analysis of 845 cases showed a higher incidence of the hypocellular type in younger patients and smaller lesions. The same subtype was significantly associated with an IC, a PS, and an SN with the latter histologic characteristics being highly correlated with each other. The surgical implications of these associations are apparent: as almost half of our cases belonged to the hypocellular subtype, it would not be exaggerated to state that surgery for PAs...
should be generally approached with caution and performed by surgeons with experience in this demanding field. The surgical margin of resection of PAs should be more generous in younger patients and in smaller lesions, with preservation of a sufficient margin of healthy tissue around them, wherever possible, for example, on the lateral side of the lesion and with the help of electromyography medial to the lesion. A younger age should by no means be an argument for being less invasive and resecting PAs with narrower margins. Especially in such cases, ED should be performed by surgeons with appropriate experience and in consideration of the particularities of PAs in this age group. In any case, how to safeguard the intactness of the capsule and achieve broad margins around the PA is a matter of philosophy, experience, and expertise.4

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