PLEOMORPHIC ADENOMA OF THE PAROTID GLAND: HISTOPATHOLOGIC ANALYSIS OF THE CAPSULAR CHARACTERISTICS OF 218 TUMORS

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Abstract: Background. Histopathologic features of the capsule may have an impact on the recurrence rate of pleomorphic adenomas.

Methods. Retrospective (n = 154) and prospective (n = 64) histologic analysis of the capsular characteristics such as incompleteness, tumor penetration, pseudopodia, and satellite tumors of 218 pleomorphic adenomas.

Results. In 160 of the 218 (73%) pleomorphic adenomas, 1 or more capsular characteristics such as incomplete capsule (33%), capsule penetration (26%), pseudopodia (40%), and satellite nodules (13%) were detected. Incomplete capsule and satellite tumors were most frequently seen in the stroma-rich (myxoid) subtype. Capsular penetration and pseudopodia were significantly more common in the prospective group than in the retrospective group (p < .05/<.05).

Conclusion. Pseudopodia and satellite tumors were more common than reported in the literature. If left in the surrounding salivary gland tissue at surgery, they can lead to recurrences of pleomorphic adenomas of the parotid gland.

Keywords: pleomorphic adenoma; parotid gland; capsular characteristics; pseudopodium; satellite tumor

Pleomorphic adenoma is the most common parotid neoplasm, accounting for about 50% of all parotid tumors.1,2 The tumors are characterized by architectural pleomorphism and composed of epithelial elements intermingled with mucoid, myxoid, or chondroid tissue.3 The standard treatment of pleomorphic adenoma is surgery. As late as the 1970s, the recurrence rate following enucleation ranged from 10% to 45%.4–7 This high rate of recurrence led to a change in surgical modality from enucleation to superficial parotidectomy, with identification and preservation of the facial nerve for pleomorphic adenomas localized in the superficial lobe. Since the introduction of this technique, the recurrence rate has decreased to 2% to 5%,5,8,9 although even a superficial or total parotidectomy involves a limited enucleation at some point in the surgical procedure in most cases, usually along the facial nerve. The most likely hypothesis for recurrence of pleomorphic adenomas is subtotal primary tumor removal due to the characteristics of the capsule, such as incompleteness, pseudopodia, and satellite nodules. Despite this implication, however, only a few papers have systematically analyzed the histo-
logic aspects of the capsule of pleomorphic adenomas. The aim of the present study was to analyze the histologic characteristics of the capsules of primary pleomorphic adenomas of the parotid gland for their relationship with histologic tumor subtype and tumor size. Furthermore, we propose clear-cut definitions of capsular characteristics to aid comparison of results of studies on pleomorphic adenoma.

PATIENTS AND METHODS

Between January 1985 and July 2006, 318 patients with the histopathologic diagnosis of pleomorphic adenoma of the parotid gland were treated at our institution. Patients with recurrent pleomorphic adenoma or who had undergone previous parotid gland surgery were excluded (n = 54). Also excluded were all pleomorphic adenomas in which the whole circumference was not histologically ascertainable on at least 2 slides (n = 46).

Thus, 218 patients with a primary pleomorphic adenoma of the parotid gland were included in the study. Eighty-seven were men and 131 women, and their mean age was 47 years (range, 20–92 years). Thirty-three (15%) of the patients were younger than 30 years, 15 male and 18 female. Deep lobe tumors (n = 29) were treated by total parotidectomy, and tumors in the superficial lobe (n = 189) by superficial parotidectomy with facial nerve preservation.

Of the 218 pleomorphic adenoma patients studied, the histologic slides of 154 were analyzed retrospectively, and 64 were enrolled in a prospective protocol. In the retrospective series, the number of histologic slides per tumor varied from 2 to 8. In the prospective series, the medial surface of the excised parotid gland (facial interface) was inked so that a probable capsular dissection could be recognized. The parotid lobe with the tumor was then cut into whole-organ sections every 2 or 3 mm. At each level, at least 1 section was processed for microscopic examination. The number of sections varied from 5 to 18 per gland. Tumor size was assessed by direct measurement of the histologic section, and the tumors were classified as smaller than 2 cm, from 2 cm to 4 cm, and larger than 4 cm. The tumors were divided into 3 histologic subtypes according to the classification of Seifert et al: the classic subtype with a stroma content of 30% to 50%; the stroma-rich (myxoid) subtype with a stroma content of 80%; and the cellular subtype with a stroma content of 20% to 30% or less. Each histologic section was examined.
for capsular integrity, capsular penetration, and
the presence or absence of pseudopodia and satel-
line tumors.

The follow-up varied from 4 to 20 years (average 9.6) in the retrospective group and from 1 to
42 months (average, 16) in the prospective group.

Two patients developed a recurrence after 5
and 8 years. The initial tumors were both located
in the superficial lobe, and the histologic types
were stroma-rich and classic. In 1 tumor, a capsu-
lar penetration was observed. In the other case,
the tumor capsule was accidentally ruptured dur-
ing initial surgery.

Nomenclature of Capsular Characteristics. Capsular
characteristics were described as follows:

Incomplete capsule designates a partial ab-
sence of encapsulation of the pleomorphic ade-
noma, with tumor tissue merging with salivary
gland tissue (Figure 1A) or fat (Figure 1B).

Capsule penetration indicates infiltration of
the fibrous tumor capsule by tumor tissue (Figure
2) without separation of the infiltrating tumor tis-
sue from the main tumor mass by fibrous fibers. In
cases with extensive capsular infiltration, the terms herniation,\textsuperscript{11} tumor buds,\textsuperscript{4} or nodular pro-
trusion\textsuperscript{14} are applied in the literature.

A pseudopodium is a tumor nodule separated
by fibrous tissue from the main tumor mass but
localized within the main tumor capsule or in con-
tact with it (Figures 3A and 3B).

Satellite nodules are distinct tumor nodules in
the vicinity of the main tumor lump but separated
from it by salivary or fat tissue without any con-
nection with the main tumor (Figures 4A and 4B).

RESULTS

The greatest axis of the tumor was smaller than
2 cm in 95 (44\%) specimens, between 2 and 4 cm
in 110 (50\%), and greater than 4 cm in 13 (6\%).

FIGURE 3. Whole-organ section of pleomorphic adenomas
with pseudopodia. (A) Classic subtype; pseudopodium in con-
tact with the main tumor capsule; the pseudopodium is not
completely encapsulated (hematoxylin-eosin stain, original mag-
nification \times1). (B) Cellular subtype; pseudopodium in contact
with the main tumor Capsule (hematoxylin-eosin stain, original
magnification \times1). [Color figure can be viewed in the online
issue, which is available at www.interscience.wiley.com.]

FIGURE 4. Whole-organ sections of pleomorphic adenomas
with satellite nodules. (A) Stroma-rich subtype with satellite
nodule (hematoxylin-eosin stain, original magnification \times0.5).
(B) Cellular subtype with pseudopodium (arrow) and satellite
nodule (hematoxylin-eosin stain, original magnification \times0.5).
[Color figure can be viewed in the online issue, which is avail-
able at www.interscience.wiley.com.]
The histologic subtype was stroma-rich in 60 (28%) specimens, classic in 114 (52%), and cellular in 44 (20%).

In the prospective series, a capsular dissection of an estimated 5% to 40% of the surface had to be performed in 51 of 64 (80%) tumors because of branches of the facial nerve (n = 49) or subcutaneous tumor localization (n = 2). In 8 cases of the prospective series, the dissection between tumor and nerve branches was performed with the help of the microscope. The mean maximum capsule thickness of 7 deep lobe tumors was 0.26 mm versus 0.217 mm of 57 superficial lobe tumors. The 10 cellular subtypes presented a mean maximum capsule thickness of 0.393 mm, the 54 stroma-rich subtypes of 0.196 mm.

Incomplete Capsule. Focal absence of the capsule with tumor tissue merging with surrounding normal parotid gland tissue (Figures 1A and 1B) or with fat cells was observed in 71 of the 218 (33%) specimens. The stroma-rich subtype had the highest rate of incomplete capsule (Table 1). No association between tumor size and capsular integrity was noted (Table 2).

Capsular Penetration. Tumor penetration of the capsule (Figure 2) was present in 57 of the 118 (26%) specimens, significantly more often in the cellular rich and classic subtypes than in the stroma-rich subtype (p < .05). No correlation between tumor size and the rate of capsular penetration was observed (Table 2).

Pseudopodia. Pseudopodia were seen in 88 of the 218 (40%) specimens (Figures 3A and 3B). In a few, the pseudopodia were not completely surrounded by a capsule (Figure 3A). Pseudopodia were more common in the classic and cellular subtypes than in the stroma-rich subtype (Table 1). There was no correlation between tumor size and presence of pseudopodia (Table 2).

Satellite Nodules. Satellite nodules (Figures 4A and 4B) (representing independent tumor foci in the salivary gland tissue) were detected in 29 of the 218 (13%) specimens. No correlation between histologic subtype and occurrence of satellite tumors was observed (Table 1). In contrast, the larger the tumor, the more often satellite nodules were observed. The difference between tumors smaller than 2 cm and tumors larger than 4 cm is statistically significant (p < .05) (Table 2).

Comparison Between the Prospective and Retrospective Study. Tumor penetration of the capsule, pseudopodia, as well as the presence of satellite tumors were all more frequent in the prospective study (Table 3). The difference was statistically significant for the rates of capsular penetration (p < .05) and of pseudopodia (p < .05).

DISCUSSION

Even the performance of a superficial or total parotidectomy involves a limited enucleation or capsular dissection at some point in the surgical pro-

<table>
<thead>
<tr>
<th>Capsular characteristics</th>
<th>Stroma-rich subtype (n = 60)</th>
<th>Classic subtype (n = 114)</th>
<th>Cellular subtype (n = 44)</th>
<th>Overall (n = 218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete capsule</td>
<td>28 (47)</td>
<td>37 (32)</td>
<td>6 (14)</td>
<td>71 (33)</td>
</tr>
<tr>
<td>Capsular penetration</td>
<td>2 (3)</td>
<td>42 (37)</td>
<td>13 (29)</td>
<td>57 (26)</td>
</tr>
<tr>
<td>Pseudopodia</td>
<td>17 (28)</td>
<td>53 (46)</td>
<td>18 (41)</td>
<td>88 (40)</td>
</tr>
<tr>
<td>Satellite nodules</td>
<td>11 (18)</td>
<td>15 (13)</td>
<td>3 (7)</td>
<td>29 (13)</td>
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</tbody>
</table>

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<tr>
<th>Capsular characteristics</th>
<th>Tumors smaller than 2 cm (n = 95)</th>
<th>Tumors between 2 and 4 cm (n = 110)</th>
<th>Tumors greater than 4 cm (n = 13)</th>
</tr>
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<tbody>
<tr>
<td>Incomplete capsule</td>
<td>25 (26)</td>
<td>40 (36)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Capsular penetration</td>
<td>20 (21)</td>
<td>35 (32)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Pseudopodia</td>
<td>38 (40)</td>
<td>45 (41)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Satellite nodules</td>
<td>9 (9)</td>
<td>16 (15)</td>
<td>4 (31)</td>
</tr>
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</table>
procedure, usually along the facial nerve. In our prospective series, a limited capsular dissection was performed in 51 of the 64 (80%) patients. Limited capsular dissection by total or superficial parotidectomy is reported to occur in between 56% and 81% of pleomorphic adenomas.9,15,16 The most probable hypothesis for recurrence of pleomorphic adenomas is subtotal primary tumor removal due to the characteristics of the capsule. Despite this attribution, however, only a few authors have systematically studied the histologic features of the capsules of pleomorphic adenomas.4,8,10–12,15 In 1976, Naeim et al4 retrospectively studied the histologic slides of 99 patients with pleomorphic adenomas. In 1990, Lam et al12 performed a study of 15 pleomorphic adenomas using whole-organ sectioning. In 1998, Henriksson et al8 observed pseudopodia in 5 of 9 (55%) pleomorphic adenomas with subsequent recurrence and in 16 of 197 (8%) without subsequent recurrence. In 2001, Stennert et al11 carried out a prospective histologic study on 100 consecutive patients with pleomorphic adenomas of the parotid gland, and in 2001 Webb et al15 performed a retrospective histologic study of 126 primary pleomorphic adenomas.

Incomplete Capsule. According to the literature, the stroma-rich (myxoid) subtype shows a higher rate of incomplete capsule (69%–71%) than the classic and cellular subtypes (11%–43%).4,11,15 In the present study, the rates of incomplete capsule were 47% and 14% for the stroma-rich and cellular subtypes, respectively. In 2004, Stennert et al11 performed semiquantitative measurements that showed capsule-free areas to comprise approximately 4% of the overall tumor circumference for all tumor subtypes. Moreover, measurements of the capsule thickness in a number of studies revealed a thicker capsule in cellular pleomorphic adenomas4,11,15 in accordance with our findings. In contrast to Harney et al17 we could not demonstrate a significant difference in capsule thickness between deep and superficial tumors. It has also been observed that small tumors possess thicker capsules than larger ones.15

Capsular Penetration. Besides the present study, only 2 others have systematically analyzed capsular penetration, reporting it in 30% to 42% of pleomorphic adenomas.4,15 Cellular subtypes are more likely to exhibit capsular penetration than stroma-rich subtypes: 42% versus 8% in the study of Naeim et al8 and 29% versus 3% in the present analysis.

Pseudopodia and Satellite Nodules. Pseudopodia were detected in 88 of the 218 (40%) tumors. We did not observe a relationship between tumor subtype and the rate of occurrence of pseudopodia. If enucleation is performed, pseudopodia may present an important risk factor for recurrence since they may be sheared off, resulting in incomplete removal (Figure 5). Unlike Stennert et al11 who only rarely observed satellite nodules and there-

<table>
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<th>Prospective group (n = 64)</th>
<th>Retrospective group (n = 154)</th>
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<td>Incomplete capsule</td>
<td>19 (30)</td>
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<tr>
<td>Pseudopodia</td>
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<td>48 (31)</td>
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<tr>
<td>Satellite nodules</td>
<td>11 (17)</td>
<td>17 (11)</td>
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FIGURE 5. Whole-organ section of a superficial parotid lobe 3 weeks after enucleation performed in a district hospital. (A) Enucleation has left a nodule in the surrounding salivary gland tissue (arrow) (hematoxylin-eosin stain, original magnification ×1). (B) High-power view of the left nodule (hematoxylin-eosin stain, original magnification ×1). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
fore listed them together with pseudopodia, we analyzed them separately, detecting satellite nodules in 29 out of 218 (13\%\textsuperscript{1}) specimens (Table 1). For the sake of correctness, it must be stated here that it cannot be ruled out that the satellite nodules in several of our cases may have represented pseudopodia projecting into the surrounding parotid tissue where they gave the impression of being a satellite nodule. Furthermore, it is sometimes difficult to differentiate between a pleomorphic adenoma with a satellite nodule originating from its main tumor and a multicentric pleomorphic adenoma. According to the literature, multicentric pleomorphic adenoma is rare.\textsuperscript{16–20}

Satellite nodules as well as long finger-like pseudopodia projecting into the surrounding parotid tissue could be left not only by enucleation but also by extracapsular dissection (Figure 6). In our 218 patients, 48\% (n = 104) of the tumors presented pseudopodia and/or satellite tumors, whereas in 2 other studies the reported rates were 28\%\textsuperscript{10} and 72\%.\textsuperscript{11} This difference can probably be explained by the application of different definitions of pseudopodia and satellite tumors; in many papers, terms regarding capsules characteristics (capsular penetration, nodular protrusion, tumor bud, herniation, satellite bud, bosselation, pseudopodium) are not clearly defined.

Comparison between the Prospective and the Retrospective Series. It is not surprising that most of the capsular characteristics we analyzed were detected more frequently in the prospective than in the retrospective series, the difference even attaining statistical significance for capsular penetration and pseudopodia (Table 3). In our prospective series, the 70\% rate of pseudopodia and/or satellite nodules (45 out of 64 tumors) is much higher than the 28\% rate in the prospective study by Stennert et al.\textsuperscript{11}

CONCLUSIONS

Focal capsular exposure was observed in 80\% of pleomorphic adenomas in the prospective series, most often because of the close anatomic relation between tumor and facial nerve branches. One or more capsular characteristics (incomplete capsule, capsular penetration, pseudopodia, and satellite nodules maybe compromising a complete tumor resection by several surgical techniques) were detected in 73\% of the 218 pleomorphic adenomas studied. Larger tumors presented more frequently with satellite nodules than smaller tumors. Pseudopodia and satellite nodules appear to be more common than presumed by other authors. There is a sometimes statistically significant difference between the results of the prospective and the retrospective study groups.

REFERENCES


