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Matrix Metalloproteinase-9 (MMP-9) Expression in Different Subtypes of Ameloblastoma

Rachmitu Anne · Ening Krisnawati · Chusni Chotimah · Benny Sjarief Latief

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Abstract
Background Ameloblastoma is a common benign odontogenic tumor of the jaw with a local invasive and highly destructive behavior and can develop in any age, with peak prevalence in 3rd-4th decade. Ameloblastoma can be divided into six histological types: follicular, plexiform, acanthomatous, desmoplastic, granular, and basal cell. Matrix metalloproteinase-9 (MMP-9) (92-kd gelatinase/ type IV collagenase = gelatinase B) is involved in bone resorption by degradation of extracellular matrix and osteoclasts recruitment. Recent studies have found that MMP-9 is expressed by ameloblastoma and has a role in ameloblastoma local invasiveness.

Objective To analyze MMP-9 expression between different histological types of ameloblastoma.

Material and method Forty samples of ameloblastoma were collected through consecutive sampling and the MMP-9 expression was detected using immunohistochemistry.

Result All samples showed positive MMP-9 expression with moderate to strong intensity. 82.4 % plexiform type and 83.3 % mixed type have strong immunoreaction. There is significant difference with follicular type with only 36.4 % (P < 0.05).

Conclusion Ameloblastoma plexiform and mixed type have higher MMP-9 expression than ameloblastoma follicular type. Different MMP-9 expression may contribute in different ameloblastoma biological behavior.

Keywords Ameloblastoma · Histological subtypes · MMP-9 · Local invasion

Introduction
Ameloblastoma is a common odontogenic tumor of the jaw that comprises 11 % of all odontogenic tumors. Ameloblastoma can be found in any ages with peak prevalence in the 3rd-4th decade of life [11]. The World Health Organization (WHO) classified ameloblastoma as benign odontogenic tumor formed by odontogenic epithelium with fibrous mature stroma but without odontogenic ectomesenchyme [2]. Ameloblastoma is classified as solid or multicystic type, unicystic type, peripheral type, and desmoplastic type. According to the histological pattern, ameloblastoma can be divided into follicular type, plexiform type, acanthomatous type, granular type, basal cell type, and desmoplastic type. A review of the international literature by Rechart et al. [3] found the solid or multicystic variant to be most common, comprising 92 % of the 3,677 cases of ameloblastoma in their review, while the unicystic and peripheral variants accounted for 6 % and 2 % of the cases. From histological pattern, the most common types are follicular (33.9 %), plexiform (30.2 %), and mixed histological type (15.5 %). Ameloblastoma is a slow-growing benign tumor but locally invasive and highly destructive with a high risk of recurrence. Ameloblastoma cells can invade into the cancellous bone beyond the tumor margin [4–7]. It is recommended to perform a radical resection 1–2 cm from tumor margin to prevent recurrences.

Pinheiro et al. [8] in their study on ameloblastoma local invasiveness found that almost half of ameloblastoma cells
Conclusion

MMP-9 is expressed by ameloblastoma cells with variation among subtypes. Ameloblastoma plexiform and mixed type have a higher MMP-9 expression than other subtypes, thus they are more invasive than follicular type. But this result should be investigated further with other methods and markers and with more samples including all six ameloblastoma histological types.

References

Table 1 Clinical information of ameloblastoma histological subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleomorphic</td>
<td>11</td>
<td>27.5</td>
</tr>
<tr>
<td>Follicular</td>
<td>17</td>
<td>42.5</td>
</tr>
<tr>
<td>Mixed</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>100</td>
</tr>
</tbody>
</table>

Age range of the patients was 11-58 years with mean age of 35.4 year.

Follicular type with >50 % immunopositive cells were only 54.5%. The staining intensity in follicular type was weak to strong staining. Immunoreact for pleomorphic type and mixed type were higher than follicular type. There was a statistically significant difference in MMP-9 immunoreact for between pleomorphic type, follicular type, and mixed type ameloblastomas (P = 0.017).

Discussion

Ameloblastoma is a benign odontogenic tumor with locally invasive and highly destructive behavior that is commonly found in the third and fourth decades of life. Ameloblastoma is divided into six histological subtypes. The difference in behavior between the subtypes is still unclear. Some researchers state that there is no correlation between histological subtypes, clinical symptoms or biological behavior. But other researchers revealed some correlation between the histological subtypes, clinical and radiographical appearances [3]. Mendenhall et al. [15] stated that ameloblastoma of different histological types exhibited diverse invasion property and biological behavior. Ameloblastoma and its local invasiveness have been attracting the attention of many researchers. Qian and Huang thought that the invasive behavior of ameloblastoma is closely correlated with the bone resorption surrounding the tumor and they are two aspects of the same physiological process [13].

MMP-9 is known for mediating degradation of basement membrane and remodeling of ECM. Studies have provided compelling evidence that MMP-9 is involved in tumor growth and bone metastasis [8, 12-14, 17-21]. According to Vicente et al. [17] MMP-2 and MMP-9 are involved in angiogenesis and tumor growth, suggesting an association of the gelatinases with aggressive behavior and unpredictable clinical course in some human neoplasms. Stankovic et al. [9] found that MMP-2 and MMP-9 activity in different clinical stages of breast cancer have a significant positive association with tumor size. MMP-9 expression has also been found to correlate with the aggressiveness of head and neck carcinomas [18, 19]. MMP-9 is also considered to have an important role in bone resorption and is closely related with several osteo-destructive pathologies [8, 20, 21]. MMP-9 act not only as solubilizers of bone matrix but also as regulators of the initiation of bone resorption [8]. Study has shown that MMP-9 is produced by osteoclast in the human bone tissues and suggest that it can degrade bone collagen in concert with MMP-1 and cysteine proteases in the sub-osteoclastic microenvironment [16]. Several studies have been conducted to analyze the MMP-9 expression in ameloblastoma [8, 12-14, 20-22]. MMP-9 expression in ameloblastoma is higher than in other odontogenic cysts and keratocyst odontogenic tumor (KOT). This finding showed that ameloblastoma have a more aggressive behavior compared to other odontogenic cysts [23]. Kumamoto et al. [24] evaluated the correlation of MMP-9 in ameloblastoma tumor growth. They conclude that MMP-9 plays a role in regulation of tumor progression. According to Pinheiro et al. [8] MMP-9 also have a role in increasing tumor cells proliferation through mitogen release. Recent studies correlate MMP-9 with osteoclastogenesis caused by ameloblastoma [14]. In our study, all specimens showed positive immunoreactions to MMP-9. This is in accordance with the result of Henriques et al. [22] that found 95% of ameloblastoma having positive MMP-9 immunoassay. Most of our specimens show moderate to strong expression intensity. Yoon et al. [25] also found that ameloblastoma has

Table 2 MMP-9 immunoprofiles of ameloblastoma histological subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Immunopositive cells (%)</th>
<th>Intensity</th>
<th>MMP-9 Immunoreactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-50 %</td>
<td>&gt;50 %</td>
<td>Weak</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>0 (0)</td>
<td>3 (17.6)</td>
<td>14 (82.4)</td>
</tr>
<tr>
<td>Follicular</td>
<td>0 (0)</td>
<td>5 (25.5)</td>
<td>6 (34.5)</td>
</tr>
<tr>
<td>Mixed</td>
<td>0 (0)</td>
<td>3 (15.8)</td>
<td>9 (59.5)</td>
</tr>
</tbody>
</table>

P = 0.267

P = 0.173

P = 0.017

( ) = in percentage. * Significant difference in expression between groups.
moderate to strong intensity of MMP-9 expression. The detection results of constant expression in all of specimens lead us to the presumption that MMP-9 played an essential role in development and progression of ameloblastoma and may be associated with bone resorption cause by ameloblastoma. From three histological subtypes, we found that ameloblastoma plexiform and mixed type have higher immunopositive cells percentage than the follicular type and also higher immunoscore. We have not found previous studies that reviewed MMP-9 expression in ameloblastoma histological subtypes. The more exuberant expression of MMP-9 in plexiform type and mixed type suggest a possible participation of this protein in cell proliferation and differentiation and may explain greater bone resorption, higher invasion potential, and poorer prognosis than follicular type.
Conclusion

MMP-9 is expressed by ameloblastoma cells with variation among subtypes. Ameloblastoma plexiform and mixed type have a higher MMP-9 expression than other subtypes, thus they are more invasive than follicular type. But this result should be investigated further with other methods and markers and with more samples including all six ameloblastoma histological types.

References
