ANALYSIS OF GROWTH POTENTIAL OF ODONTOGENIC KERATOCYST USING KI-67: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: This review aims to compare scientific articles from a database that used Ki-67 immunohistochemical marker to evaluate the growth potential and biological behaviour of Odontogenic Keratocyst (OKC). Material and Methods: literature search was done in the MEDLINE/PubMed database and 8 articles were finalised for final data collection and analysis. Results: literature review showed that Ki-67 can be used to calculate the Proliferative Index of OKC and thus the biological behaviour of the lesion can be assessed. Conclusion: OKC represents specific histopathological features, a very high recurrence rate and aggressive biological behaviour. Due to these features, it poses a great challenge to oral surgeons in determining the best possible treatment modality resulting in minimum risk of recurrence and morbidity. Thus, Ki-67 can be used to assess the biological behaviour and growth potential of OKC.

Keywords- Ki-67, Odontogenic Keratocyst, Proliferative index, Biological Behaviour, Growth Potential.

I. INTRODUCTION

Philipsen in 1956 first described the term Odontogenic Keratocyst. It was classified as developmental odontogenic cysts by Pinborg and Kramer in 1971. Since then this lesion has been a point of controversy regarding its cystic or neoplastic nature. Odontogenic Keratocyst displays unique characteristics like locally destructive and aggressive behaviour, very high recurrence rate and genetic mutations in PTCH1 gene. Due to these unique features, WHO in 2005, considered the lesion as a neoplasm and named it as Keratocystic Odontogenic Tumor.1

Some researchers did not agree to the neoplastic nature of the lesion, as they were not satisfied with the existing evidence to support the lesion as neoplasm.2 In 2017, a new classification was published by WHO, in which the term KCOT was discontinued and again the lesion is placed in the cystic category with the name Odontogenic Keratocyst.3

Odontogenic Keratocyst represents 11.2% of all the odontogenic cysts that are developmental in origin and arise from the remanats of dental tissues like epithelial cell rests of malassez, cell rests of serre, reduced enamel epithelium etc.4 OKC represents specific histopathological features, a very high recurrence rate of 20-62% and aggressive biological behaviour. Due to these features it poses a great challenge to oral surgeons in determining the best possible treatment modality resulting in minimum risk of recurrence and morbidity.5,6

Cell proliferation marks the fundamental of both embryonic and postembryonic existence of all living beings. Hence, identifying the cell proliferation activity may help to evaluate the biological behaviour or growth potential of the lesion.7

Ki-67 has been found to be highly specific marker for proliferating cells and is commonly used to estimate the biological behaviour of the lesions.8 Ki-67 has been used by different researchers to investigate the cell proliferation activity in different odontogenic cysts by measuring the Ki-67 proliferation index.9

The proliferative activity of OKC has been a point of study by various researchers to understand the pathogenesis and biological behaviour of the lesion. However, since all the studies represents different proliferation index, it
becomes very difficult to get a proper knowledge about the biological behaviour of the lesion and also if Ki-67 can be used as a proliferative marker to assess the growth potential of OKC.

Hence, in this review an attempt will be made to compare scientific articles from a database that used Ki-67 immunohistochemical marker to evaluate the growth potential and biological behaviour of OKC.

II. MATERIALS AND METHOD

A literature search was conducted on the MEDLINE/PubMed database in July 2021. The search was conducted for last 10 years. Most recent articles were selected using the abstract format. The MeSH terms used were: “Ki-67”, “Odontogenic Keratocysts” and “cell Proliferation index”. Search was also done by combining with other terms: “Keratocystic odontogenic tumor”, “mitotic index” and “Keratocystic Odontogenic Tumor”.

A two staged search was performed. In first stage search was done using different combinations of keywords. The articles were chosen on the bases of titles and case reports and systematic reviews were excluded. The papers in language other than English were also excluded.

In the next search stage the papers were selected based on the inclusion and exclusion criteria. In some papers the proliferative index for both non-syndromic and syndromic OKC was given, in that case only the proliferative index for non-syndromic, solitary OKC was selected.

In the initial search 12 papers were selected based on the exclusion criteria designed for stage 1. All the results obtained by combining different keywords were compiled and the papers which appeared recurrently in different searches were considered only one time.

In the second stage, full texts of the papers were studied and the selection was made according to the inclusion and exclusion criteria, and 8 papers were selected for final data collection and analysis. Following are the exclusion and inclusion criterias:

Exclusion criteria:
1. No cell proliferation index
2. Unclear methodology
3. Impossible to reach a single PI value with the information on the paper
4. Case reports and systematic reviews
5. Studies on odontogenic cysts other than Odontogenic Keratocyst

Inclusion criteria:
1. Studies on the immunohistochemical expression levels of Ki-67 in Odontogenic Keratocysts published from 2011 to 2021
2. Full text articles available in English language.
3. Ki-67 values expressed as = Total number of cells showing Ki-67 expression x 100 Total number of cells counted
4. Clearly defined methodology
5. Single value of proliferative index
6. Original studies
III. RESULT

The selected papers represent the Ki-67 proliferation index as mean or median where 6 papers represents the mean index and 2 papers represents the median. Three paper studies the proliferation index in three layers of epithelium – basal, suprabasal and superficial, while 1 paper represents the proliferation index in only basal and suprabasal layer. In 4 papers the entire epithelium is being studied for the expression of Ki-67. In 6 papers the counting is done in 10 consecutive high power fields at x400 magnification and cells are counted in 5 fields in 2 papers. All the data collected is shown in the table 1.

Table 1- Articles showing the Proliferative Index as mean and median

<table>
<thead>
<tr>
<th>Article</th>
<th>Year</th>
<th>n</th>
<th>Mean (%)</th>
<th>Median</th>
<th>Magnification</th>
<th>Fields</th>
<th>Cells</th>
<th>Layer of epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modi et al.</td>
<td>2018</td>
<td>15</td>
<td>12.76%</td>
<td></td>
<td>x400</td>
<td>5</td>
<td>1000</td>
<td>B/SB/S</td>
</tr>
<tr>
<td>Amaral et al</td>
<td>2012</td>
<td>11</td>
<td>-</td>
<td>9.83</td>
<td>x400</td>
<td>10</td>
<td>-</td>
<td>Entire epithelium</td>
</tr>
<tr>
<td>Caetano et al</td>
<td>2012</td>
<td>20</td>
<td>18.97</td>
<td></td>
<td>x400</td>
<td>10</td>
<td>400</td>
<td>B/SB/S</td>
</tr>
<tr>
<td>Metgud et al</td>
<td>2013</td>
<td>15</td>
<td>-</td>
<td>10.91</td>
<td>x400</td>
<td>10</td>
<td>-</td>
<td>B/SB/S</td>
</tr>
<tr>
<td>Orikpete et al</td>
<td>2020</td>
<td>4</td>
<td>7.7</td>
<td></td>
<td>x400</td>
<td>5</td>
<td>-</td>
<td>Entire epithelium</td>
</tr>
<tr>
<td>Redman et al</td>
<td>2017</td>
<td>3</td>
<td>18.9</td>
<td></td>
<td>x400</td>
<td>10</td>
<td>-</td>
<td>Entire epithelium</td>
</tr>
<tr>
<td>Oliveira Ramos GD et al</td>
<td>2014</td>
<td>11</td>
<td>25.3</td>
<td></td>
<td>x400</td>
<td>10</td>
<td>1000</td>
<td>Entire epithelium</td>
</tr>
<tr>
<td>Alur J et al</td>
<td>2014</td>
<td>13</td>
<td>30.48</td>
<td></td>
<td>x400</td>
<td>10</td>
<td>1000</td>
<td>B/SB</td>
</tr>
</tbody>
</table>
IV. DISCUSSION

Odontogenic keratocyst is a benign, but locally aggressive lesion. Controversies always persisted regarding the its biological behaviour due to its aggressive nature.\textsuperscript{10} Ki-67 has been used to determine the proliferative potential of the cells of OKC in some papers, but the results obtained and the methodologies used to analyze the proliferative index are different in every paper, hence this study tries to analyze the methodologies and PI by comparing these articles.

Our literature search revealed the mean proliferation index ranging from 7.7 to 30.48 in six papers while two papers showed 9.83 to 10.43 as median. The Proliferative index (PI) of Ki-67 antibody in each paper was calculated as the total number of cells showing Ki-67 expression divided by the total number of cells counted × 100. Almost all the papers studied the cells at X400 magnification. Four papers evaluated the Ki-67 expression in the entire epithelium while three papers did in the basal, suprabasal and superficial layers of epithelium and only one paper calculated the PI in basal and suprabasal layer.

The basal and parabasal cell layers of the epithelium represent the normal cell proliferative compartment. The cellular maturation takes place in the suprabasal layers where keratin is expressed due to cellular maturation. Therefore, any sign of proliferative cellular activity beyond the parabasal layer should be considered as a matter of concern.\textsuperscript{11}

In a study by Modi et al, when all the layers of epithelium were taken into consideration, the overall Ki-67 PI was noted highest in OKC (12.76 ± 4.78) when compared to Dentigerous Cyst (5.87 ± 4.24) and Radicular cyst (5.08 ± 3.11). The expression of Ki-67 was higher in suprabasal cell layer (19.66 ± 7.89) than in basal cell layer (9.18 ± 4.79) in OKC. In Dentigerous and Radicular cysts, the Ki-67 was positive in the basal cell layer and minimal activity was noted in the suprabasal layer of the epithelium, thus suggesting that proliferative potential of OKC resides in the suprabasal cell layer.\textsuperscript{4} Orikpete, et al. and Oliveira Ramos et al also found the same result with a higher PI on OKC rather that Unicystic ameloblastoma, Radicular cyst and Dentigerous cyst. The expression of Ki-67 was mainly in the suprabasal layer of the epithelium.\textsuperscript{12,13} Since these results were similar to Modi et al, hence it can be suggested that the proliferative capacity of the cystic lining of OKCs reside within the suprabasal layer of the epithelium.

Amaral et al and Metgud et al also noted higher PI in KCOT than in Ameloblastoma,\textsuperscript{14,15} although there were many studies like Thosaporn W et al and Piatelli A et al that were in contrast to the above study stating a higher proliferation index in Ameloblastoma rather than OKC.\textsuperscript{16,17} Different method for evaluation of PI for OKC was used by all these authors.

The differences in the proliferative activity of the epithelium in OKC as compared to other odontogenic cysts is due to an atypical cell cycle, thus suggesting its aggressive biological behaviour.\textsuperscript{4}

The calculation of the percentage of cells showing the expression of Ki-67 is affected by the number of fields analyzed and the methods of their selection as random or continuous fields. The proliferative index can be affected by any parameter that can change the total number of cells counted i.e. if more number of fields are analyzed, more will be the total number of cells counted and hence greater will be the Proliferative Index.

Hence, a standard evaluation method is suggested for the future studies to assess the proliferative activity and calculation of the PI of OKC, using the same number of cells, same magnification, and evaluation of all the layers of epithelium.

V. CONCLUSION

All the data collected for this systematic review, showed that Ki-67 can be used to access the proliferative activity and the biological behaviour of OKC. In view of the various methodologies noticed during the literature search for evaluating the proliferative activity in OKC, it is worthwhile that continuing studies should aim at developing a standard evaluation methodology for assessing the biological behaviour of OKC.

REFERENCES


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