Study of various nuclear features of papillary thyroid carcinoma in other thyroid lesions

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Abstract
Introduction: Papillary thyroid carcinoma is the only thyroid malignancy that is diagnosed on the basis of its nuclear characteristics, regardless of cytoplasmic features, growth patterns or immunohistochemistry. Although nuclear features have become hallmark for the diagnosis, they are neither constant nor specific. They can be seen in other tumours and non-tumours condition of thyroid. With the aim to know the frequency of various nuclear features of papillary thyroid carcinoma in other thyroid lesions and also to find out which of the various nuclear features are most diagnostic of papillary thyroid carcinoma, this study was done.

Materials and Methods: The present study was conducted on Fine needle aspiration cytology of thyroid lesions where corresponding histopathological diagnosis was available, from 2010 to 2016. All cytology smears of were reviewed by two investigators who were blinded with respect to the final histopathological diagnosis.

Results: 155 cases were included in the study; category 2 was the most common constituting 76%, followed by category 6 which was 35%. Frequency of various nuclear features of papillary carcinoma in other thyroid categories varied from 10% to 33%

Conclusion: Frequency of various nuclear features of papillary carcinoma in other thyroid categories varied from 10% to 33% and Intranuclear cytoplasmic inclusions are the most diagnostic nuclear features of papillary carcinoma.

Keywords: Papillary thyroid carcinoma, Nuclear inclusions, Nuclear grooves, Fine granular chromatin.

Introduction
Papillary thyroid carcinoma is the only thyroid malignancy that is diagnosed on the basis of its nuclear characteristics, regardless of cytoplasmic features, growth patterns or immunohistochemistry.1 The diagnosis of Papillary Thyroid Carcinoma (PTC) depends on presence of major diagnostic nuclear features. These are enlarged crowded nuclei, fine powdery chromatin, Intranuclear cytoplasmic inclusions (INCI), nuclear grooves, micro or macronucleoli.1,3

Although nuclear features have become hallmark for the diagnosis, they are neither constant nor specific. They can be seen in many other conditions like Hashimoto thyroiditis, nodular goiter, in other primary thyroid tumors (medullary carcinoma hurthle cell neoplasms) and also in secondary tumors (malignant melanoma, bronchioalveolar carcinoma, and ovarian tumors).3,5

This study was carried out to know the frequency of various nuclear features of papillary thyroid carcinoma in other thyroid lesions and to find out which of the various nuclear features are most diagnostic of papillary thyroid carcinoma.

Materials and Methods
The present study was conducted on 155 cases of Fine needle aspiration cytology of thyroid lesions where corresponding histopathological diagnosis was available, from 2010 to 2016 in the department of pathology attached to SDUAHER. All cytology smears of were reviewed by two investigators who were blinded with respect to the final histopathological diagnosis. All smears were reexamined under low power field for the degree of cellularity, cell arrangement and amount of colloid. Each papanicolaou stained smear was carefully examined semi quantitatively under high power field (HPF) for the presence of various nuclear features. Minimum 20 cellular HPF were examined for the presence of nuclear crowding, enlarged irregular nuclei, fine granular chromatin, nuclear grooves, INCI. A score of 1 + was given if any nuclear feature was present, 2+ when nuclear feature were more than 5HPF, 3+ when nuclear feature were more than 10 HPF. All cases were reviewed based on Bethesda system for reporting thyroid cytopathology. The microscopic findings studied were entered in Microsoft office excel sheet, descriptive statistical analysis was done.

Results
The study was conducted on 155 cases of fine needle aspirations of thyroid. Category 2-76 cases, category 3-14 cases, category 4-18 cases, category 5-12 cases, category 6-35 cases. Age range was from 24-61 years. Male to female ratio was 1:5. Category 1 was excluded from the study.

Frequency of various nuclear features in all categories is shown in Table 1 and 2. Enlarged crowded nuclei were seen in 100% of PTC, where score+1, +2 were 57.14, and +3 42.85. In other thyroid categories category 3- 16.6%, category 4- 25.0% and enlarged crowded nuclei were not seen in category 1 and 2.
Fine granular (powdery) chromatin was present in all PTC. Score+1 and +2 were seen in 80% and +3 in 20%. In other thyroid categories, category 2 had 15.7% (score+1), category 3- 21.4% (score +1), category 4- 27.7%, (score+1) category 5- 33% (Score+1). INCI were seen in 100% of PTC. INCI+1, +2 were seen in 82.3% and +3- 5.7%. INCI were not found in other thyroid categories.

Nuclear grooves in papillary thyroid score +1, +2 were seen in 85.71% and +3- 14.28%. Category 5 had 20%, not seen other categories.

85% (+1) of PTC showed micronucleoli, in other categories category 2 – 10%, category 3 -21.4%, category 4- 16.6%, category 5 -33%.

**Table 1: Various nuclear features in category 2, 3, 4 and 5**

<table>
<thead>
<tr>
<th>Cytological features</th>
<th>Cat -2 n=76</th>
<th>Percentage</th>
<th>Cat -3 n=14</th>
<th>%</th>
<th>Cat -4 n=18</th>
<th>%</th>
<th>Cat -5 n=12</th>
<th>%</th>
<th>Chi-Square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crowded enlarged nucleus+1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>16.66</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine granular chromatin+1</td>
<td>12</td>
<td>15.78</td>
<td>3</td>
<td>21.4</td>
<td>5</td>
<td>27.77</td>
<td>4</td>
<td>33.0</td>
<td>42.04</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nuclear grooves+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>25</td>
<td>39.01</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>INCI</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronucleoli+1</td>
<td>8</td>
<td>10</td>
<td>3</td>
<td>21.4</td>
<td>3</td>
<td>16.6</td>
<td>4</td>
<td>33.0</td>
<td>36.67</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Table 2: Various nuclear features of papillary carcinoma in category 6**

<table>
<thead>
<tr>
<th>Cytomorphological features</th>
<th>Cat -6 n=35</th>
<th>Percentage</th>
<th>Chi Squar</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enlarged crowded nucleus+1 and +2</td>
<td>20</td>
<td>57.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarged crowded nucleus+3</td>
<td>15</td>
<td>42.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine granular chromatin+1 and +2</td>
<td>28</td>
<td>80.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine granular chromatin +3</td>
<td>7</td>
<td>20.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear grooves+1 and +2</td>
<td>30</td>
<td>85.71</td>
<td>127.01</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nuclear grooves+3</td>
<td>5</td>
<td>14.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INCI+1 and +2</td>
<td>28</td>
<td>80.0</td>
<td>125.01</td>
<td>0.0001</td>
</tr>
<tr>
<td>INCI +3</td>
<td>4</td>
<td>11.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro nucleoli+1</td>
<td>30</td>
<td>85</td>
<td>130.03</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Discussion**

Papillary thyroid carcinoma is the most common thyroid malignancy accounting to 80% of all thyroid carcinomas; they are more common in female. Most commonly seen below 40 years of age, it is the most common pediatric thyroid tumor.1,4,6

The diagnosis of papillary carcinoma on Fine needle cytology depends on presence of well recognized nuclear features irrespective of architectural pattern. They should be presenting widespread throughout the follicular cell population. Papillary carcinoma is the only tumor that is diagnosed based of nuclear features.7

The most common nuclear features are enlarged crowded nuclei, fine powdery chromatin, INCI, nuclear grooves and micro or macronucleoli. However these nuclear features lack specificity, they can be seen in many benign and malignant conditions of thyroid and also in others secondary tumors.1,4,5,8 Present study aimed to know the frequency of various nuclear features of papillary thyroid carcinoma in other thyroid lesions and to find out which of the various nuclear features are most diagnostic of papillary thyroid carcinoma. Table 3 compares various nuclear features of papillary carcinoma with other studies.

**Table 3: Comparison of present study category 6 with other studies**

<table>
<thead>
<tr>
<th>Nuclear features</th>
<th>Mallik MK et al n=61</th>
<th>Politi HD et al n=37</th>
<th>Mittendorf EA et al n=45</th>
<th>Bhat A et al n=21</th>
<th>Rani D et al n=32</th>
<th>Present study n=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>crowded enlarged nucleus</td>
<td>97%</td>
<td>77</td>
<td>100</td>
<td>97</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Fine granular chromatin</td>
<td>95%</td>
<td>95%</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Nuclear grooves</td>
<td>55%</td>
<td>92%</td>
<td>94.4</td>
<td>100</td>
<td>46</td>
<td>100</td>
</tr>
<tr>
<td>INCI</td>
<td>93%</td>
<td>92%</td>
<td>94.4</td>
<td>23</td>
<td>93</td>
<td>91.42</td>
</tr>
<tr>
<td>Micronucleoli</td>
<td></td>
<td></td>
<td></td>
<td>53</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

In the present study, all the aspirates of papillary carcinoma showed enlarged crowded nuclei (Fig 1). 57.14% of papillary carcinoma showed score+1 and +2, and score 3+ was 42.85%. Similar to our study, enlarged crowded nuclei were significant findings in a study done by Bhat A et al.9 Rani et al,10 and Kunjumon...
and Upadhyaya,11 where they reported that enlarged crowded nuclei were seen in 100% of papillary carcinoma cases.  

Fine granular (powdery) chromatin (Fig. 2) was present in all the papillary thyroid carcinoma. +1 and +2 were seen in 80% and +3 in 20%. Similar finding were noted by Bhat A et al9 and Rani et al10 where they have reported 100% of PTC had fine granular chromatin. This chromatin change can be seen in aspirates containing large amount of peripheral blood, which hinders proper fixation of smears, can be avoided by using thinner gauge needle and limiting number of passes.15  

Intranuclear cytoplasmic inclusions are the most valuable diagnostic nuclear Feature of papillary carcinoma (Fig. 3). It was first reported by Soderstrom and Bjorkland in 1973.13 These are crisp, clear, can vary in number; margins are usually sharp and distinct. Density and texture is similar to the cytoplasm, better seen in Papanicolaou stains.1,4,14 Presence of more than three intranuclear inclusions seen in enlarged nuclei on a single thyroid aspirate is diagnostic of papillary thyroid carcinoma.15 These should not be confused for clear areas in the nucleus which are usually artifacts.1,13,15,16 In the present study INCI+1, +2 were seen in 82.3% and 5.7% (+3) and not found in other thyroid categories. P value was 0.0001, highly significant. Rani et al10 in her study reported in 93.8% cases of papillary thyroid carcinoma. Kini et al17 in 83% of histologically proven papillary thyroid cancer, and while Sharma et al18 in 86.5% of cases. Studies have shown that they can be seen in benign non papillary thyroid lesions.19,20 In a study done by Pandey et al,21 where they have studied 447 thyroid aspirates, the reason behind wrong diagnosis of some cases was due to too much emphasis on intranuclear inclusions and they have told that although typical nuclear alterations help in the diagnosis of PTC, none of them are diagnostic in isolation or low frequency. They are diagnostic when they are widespread and in combination.  

Nuclear grooves (Fig. 2 and 4) which are nothing but invagination of the nuclear membrane that will traverse the entire longitudinal axis of the nucleus are another important nuclear feature of papillary carcinoma.1,4,5,22 In the present study, in papillary carcinoma nuclear grooves +1, +2 was seen in 87.71% and +3 14.28% (+3). P value was 0.0001 highly significant. Bhat et al10 in her study had similar results, in other studies frequency varies from 46% to 94%. Nuclear grooves in other thyroid categories were shown in table 1. In a study done by Mallik et al,8 nuclear grooves were not seen in category 2 and 4, while category 5 had -20% and they have said that grooves can be regarded as useful cytomorphological feature in the diagnosis of papillary thyroid carcinoma. Sharma et al18 observed in 78% of papillary thyroid carcinoma. In a study done by Politi HD22 nuclear grooves were seen in 92% of papillary carcinoma thyroid, only two of 50
case of follicular neoplasms, they were present in small number and the authors believed that nuclear grooves were a very useful criterion in the diagnosis of PTC by fine needle aspiration biopsy. In a study done by Scopa CD et al,23 they have said that nuclear grooves are not restricted to papillary carcinoma, they can present in various thyroid lesions.  

Nucleolus may be small and large. Can be single or multiple. In the present study 85% (+1) of papillary carcinoma showed micronuleoli (Fig. 4). In other studies, Bhat A et al9 had 100%, Rani et al10 53.1%.
Various nuclear features of papillary carcinoma can be seen in other lesions of thyroid, but the percentage is really less. When strict morphological feature of each nuclear feature is kept in mind and seen the smears, they help in categorization and diagnosis of papillary carcinoma. The diagnosis of PTC should be based on all nuclear features rather than single feature. From the present study, we conclude that frequency of various nuclear features of papillary carcinoma in other thyroid categories varied from 10% to 33% and intranuclear cytoplasmic inclusions are the most diagnostic nuclear features of papillary carcinoma.

Conflicts of Interest: Nil

References

15. Yang GC, Greenbaum E. clear nuclei of papillary thyroid carcinoma are conspicuous in fine needle aspiration and intraoperative smears processed by ultrafast Papanicolaou stain. Mod Pathol. 1997;10(6):552-555.

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