CLINICOMORPHOLOGICAL SPECTRUM OF THYROID LESIONS WITH FOLLICULAR PATTERN ON MICROSCOPY

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ABSTRACT

Objective: To histopathologically evaluate thyroid lesions with follicular pattern on routine microscopy.
Study Design: Descriptive cross sectional study.
Place and Duration of Study: The cross sectional study was carried out at the department of Pathology PNS Shifa, Karachi, between January 2013 to January 2014.
Material and Methods: Total of 84 patients presenting with thyroid lesions with follicular pattern on hematoxylin and eosin (H&E) staining and having age between 18-60 years were included by non probability consecutive sampling technique. SPSS version 10 was used for statistical analysis.
Results: Out of 84 cases, 52 (61.90%) were between age 18-40 years, 32 (38.10%) were between 41-60 years of age, with mean ± standard deviation (sd) as 37.10 ± 8.24 years but 62 (73.81%) of the patients presented with the duration of the illness between 1-6 months and 22 (26.19%) of the patients presented with the duration of the illness between 7-12 months within mean ± sd as 5.26 ± 2.53 months. Thirteen (15.47%) were males, 33 (39.29%) had follicular adenoma, 38 (45.24%) had micro follicular adenomatoid nodule, 9 (10.71%) had micro follicular adenomatoid nodule in background of thyroiditis while 4 (4.76%) had follicular carcinoma.
Conclusion: Follicular pattern can be seen both in benign and malignant lesions of thyroid gland. Microfollicular adenomatoid nodule and follicular adenoma are the frequent thyroid gland lesions presenting with follicular pattern on routine histopathological examination. Proper identification of these lesions and differentiation from malignant lesion such as follicular carcinoma is required for the management of the morbidity. In this regard, meticulous microscopic examination and immunohistochemistry is required for the proper diagnosis of the lesion.

Keywords: Follicular adenoma, follicular adeno carcinoma, neoplasm, thyroid gland, thyroid nodule.

INTRODUCTION

Thyroid gland is one of the largest endocrine glands. The thyroid gland is made up of two types of cells. These are follicular cells and parafollicular cells. Major portion of thyroid gland is made up of follicular cells and these cells secrete iodine-containing hormones called thyroxine (T4) and triiodothyronine (T3). The parafollicular cells secrete the hormone calcitonin. The follicular lesions of thyroid are common and are broadly classified as benign and malignant lesions. Amongst the benign lesions, it includes hyperplastic nodules, adenomatoid nodules and follicular adenoma. The malignant counterparts are follicular carcinoma and follicular variants of papillary carcinoma[1]. In general population, there is an estimated 4-7 percent prevalence of goitre worldwide whereas the incidence of malignancy is about 10 percent in goitrous thyroid[2]. Diagnosing the follicular lesions of thyroid poses a great challenge to the histopathologists as there are certain lesions which cannot be categorized as definite benign or malignant lesions on routine examination of heamtoxylin-eosin stained slides. These lesions represent a “grey zone"[2]. In such cases, immuno histochemistry plays a vital role in establishing various follicular lesions as benign or malignant and for further sub-classification. Immuno histochemical markers like vimentin, pankeratin, thyroglobulin and TTF1 positivity are consistent with a follicular differentiation[3]. Follicular adenoma shows significantly higher

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expression of CD 56 and E-Cadherin, whereas follicular carcinoma shows expression of HBME-1[4].

In a study which was conducted in Brazil, out of 197 patients whose thyroid lesions were diagnosed as follicular lesion of undetermined significance, the histopathologic follicular lesions of thyroid turned out to be as follows: Sixty five turned out to be of follicular adenoma which makes a percentage of 32.9%, 81 cases (41.0%) were of microfollicular adenomatoid nodule, 19 (9.6%) were of microfollicular adenomatoid nodule having background of thyroiditis, 17 (8.6%) cases were follicular carcinoma, 9 (4.6%) cases were of follicular variant papillary carcinoma, and 6 (3.1%) cases were of classic papillary carcinoma, with a 16.2% incidence of malignancy[5]. In Pakistan, the frequency of follicular carcinoma is 2% with a female-to-male ratio of 4.7:1. The patients with maximum number are reported to be in the fourth decade of life followed by the third and second decades[6]. The follicular neoplasm is a frequent indication for surgery of the thyroid gland. The role of intraoperative frozen section to differentiate between benign and malignat neoplasms is not encouraging. There are chances of missing certain lesions of follicular neoplasms[7] and a detailed histopathological evaluation of the resected specimen is required to look for type of lesion / tumor, capsular invasion and vascular invasion which has a definite impact on outcome of the disease.

The rationale of this study was to evaluate different variants of follicular lesions of thyroid (benign / malignant).

MATERIAL AND METHODS

This cross sectional descriptive study was conducted at the department of pathology, PNS Shifa, Karachi from Jan 2013 to Jan 2014. Formal approval of study from hospital ethical committee was sought. All specimens of thyroid tissue having follicular pattern on routine hematoxylin and eosin (H&E) sectioning, patients from both genders (male and female), patients from 18-60 years of age groups and all fresh cases of thyroid lesions who were not diagnosed or treated previously for any thyroid pathology were included. Biopsy of thyroid gland tissue having lesion other than follicular pattern and poorly fixed / autolyzed specimens were excluded. Sample size was calculated as 84 patients by WHO calculator where, confidence level was 95%, anticipated population proportion was 8.6%, absolute precision required was 6%. Eighty four patients were included through non probability consecutive sampling. Informed consent was obtained from the patients prior to surgery for laboratory evaluation of surgical specimen. All the resected thyroidectomy specimens along with request form for histopathological examination submitted to histopathology department of PNS Shifa hospital and fulfilling the inclusion criteria was fixed in 10% buffered formalin and allowed to stay overnight, then examined grossly. Specimens were measured in three dimensions and weighed. After paraffin embedding slides were prepared and stained with H&E. Detailed evaluation of the lesion was done for type of follicular lesion by two pathologists independently. Lesions like follicular adenoma, microfollicular adenomatoid nodule or microfollicular adenomatoid nodule in the background of thyroiditis or follicular carcinoma were considered according to standard histological criteria. Patient's name, age, gender, duration of illness and type of follicular lesion was recorded in a proforma. The data were analysed using SPSS version 10. Frequencies and percentages were computed for qualitative variables like gender, type of follicular lesion. Mean ± standard deviation were calculated for quantitative variables like age of the patients and duration of thyroid lesions. A p value of <0.05 was considered as significant. Stratification with respect to age, duration of thyroid lesions and gender was done.

RESULTS

A total of 84 cases were enrolled. Fifty two (61.90%) were between 18-40 years and 32

(38.10%) were between 41-60 years, with average age of 37.10 ± 8.24 years. Seventy one (84.53%) were female. Majority (73.81%) patients had duration of illness of ≤6 months (shown in table-I). Frequency of various thyroid gland lesions presenting with follicular pattern on histopathological examination reveals that 33 (39.29%) were with follicular adenoma, 38 (45.24%) had microfollicular adenomatoid nodule, 9 (10.71%) had microfollicular adenomatoid nodule in background of thyroiditis while 4 (4.76%) had follicular carcinoma.

Table-I: Description of duration of illness (n=84).

Duraion of illness (months)	No. of Patients	Percentage
Mean ± SD	5.26% ± 2.53	
1-6	62	73.81
7-12	22	26.19

Table-II: Description of types of lesions according to age, gender and duration of illness.

	Follicular Adenoma (n=33)	Microfollicular Adenomatoid Nodule (n=38)	Microfollicular Adenomatoid Nodule In Background of Thyroiditis (n=9)	Follicular Carcinoma (n=4)	*p*-value
Age (Years)					
18-40	23 (69.70%)	21 (55.26%)	5 (55.56%)	3 (75%)	<0.001
41-60	10 (30.30%)	17 (44.74%)	4 (44.45%)	1 (25%)	
Gender					
Male	6 (18.18%)	4 (10.53%)	2 (22.22%)	1 (25%)	<0.001
Female	27 (81.82%)	34 (89.47%)	7 (77.78%)	3 (75%)	
Duration of illness (months)					
≤6	25 (75.76%)	29 (76.32%)	7 (77.78%)	1 (25%)	<0.001
>6	8 (24.24%)	9 (23.68%)	2 (22.22%)	3 (75%)	

Stratification for age was done which shows that out of 33 cases of follicular adenoma 69.70% (n=23) were between 18-40 years while 30.30% (n=10) were between 41-60 years, (*p*-value 0.001), out of 38 cases of microfollicular adenomatoid nodule 55.26% (n=21) were between 18-40 years and 44.74% (n=17) were between 41-60 years, (*p*-value 0.35), out of 9 cases of microfollicular adenomatoid nodule in background of thyroiditis 55.55% (n=5) were between 18-40 years and 44.45%(n=4) were between 41-60 years, (*p*-value 0.43) while out of 4 cases of follicular carcinoma 75% (n=3) were between 18-40 years and 25%(n=1) were between 41-60 years of age, (*p*-value <0.001), (table-II).

Stratification for gender was done which shows that out of 33 cases of follicular adenoma 18.18% (n=6) were male and 81.82% (n=27) were females, (*p*-value <0.001), out of 38 cases of microfollicular adenomatoid nodule 10.53%(n=4) were male and 89.47% (n=34) were females, (*p*-value <0.001), out of 9 cases of microfollicular adenomatoid nodule in background of thyroiditis 22.22% (n=2) were male and 77.78% (n=7) were females, (*p*-value <0.001) while out of 4 cases of follicular carcinoma 25% (n=1) were male and 75% (n=3) were females, (*p*-value <0.001).

Stratification for duration of illness was done which shows that out of 33 cases of follicular adenoma, 75.76% (n=25) were having symptoms in between 1-6 months while 24.24% (n=8) were having symptoms between 7-12 months, (*p*-value <0.001), out of 38 cases of microfollicular adenomatoid nodule 76.32% (n=29) were having symptoms between 1-6 months and 23.68% (n=9) were having symptoms between 7-12 months, (*p*-value <0.001), out of 9

cases of microfollicular adenomatoid nodule in background of thyroiditis 77.78% (n=7) were having symptoms between 1-6 moths and 22.22% (n=2) were having symptoms between 7-12 months, (*p*-value <0.001) while out of 4 cases of follicular carcinoma 25% (n=1) were having symptoms between 1-6 months and 75% (n=3) were having symptoms between 7-12 months, (*p*-value <0.001).

DISCUSSION

Thyroid nodules are common entity in routine clinical practice and they are present in 4-7% of the population, however, this percentage can increase on use of ultrasonography[8]. Females are affected four times more than males and these thyroid nodules can be caused by a variety of thyroid disorders[8-9]. The term follicular in thyroid specimens is used by pathologists to designate cell of origin, ie. lesions of follicular cell origin (capable of producing thyroid hormone and thyroglobulin) and to describe the architecture or growth pattern, i.e. follicular patterned.

By light microscopy, a thyroid lesion is designated as follicular when it totally or almost totally (more than 95%) displays a follicular growth pattern, or thyroid follicles with a central lumen containing variable amounts of colloid. The follicles are classified further on the basis of their size as microfollicles or macrofollicles; although some lesions display a mixture of large and small follicles, usually one pattern predominates. Further classification of these lesions involves separation on the basis of encapsulation (totally encapsulated, partially encapsulated, or unencapsulated).

The lack of a capsule is more common in nonneoplastic follicular (hyperplastic, adenomatous) nodules, whereas neoplastic nodules tend to be encapsulated.

In our study majority of patients, 61.90% were between 18-40 years of age and 38.10% were between 41-60 years, mean ± sd was calculated as 37.10 ± 8.24 years. Whereas in another study, 55.14% of patients were between 45-92 years of age and 44.86% of the patients were between 13-45 years[11]. Most of the cases presented with duration of the illness between 1-6 months, 73.81%. Whereas 26.19% of the patients presented with the duration of the illness between 7-12 months, mean ± sd was calculated as 5.26 ± 2.53 months. Majority of the cases were females, (84.53%). Whereas, the percentage of females was 84.93% in another study[11]. Benign lesions such as follicular adenomas, microfollicular adenomatoid nodule and microfollicular adenomatoid nodule in back-ground of thyroiditis was seen in about 93% of the cases and only 4.76% had follicular carcinoma. In comparison, the study which was carried out in Brazil revealed that out of 197 patients whom thyroid lesions were diagnosed as follicular lesion of undetermined significance, the histopathologic follicular lesions of thyroid turned out to be malignant in about 16.2% of the cases[5].

However, a retrospective study of patients with multinodular goiter with one or more dominant nodules who underwent ultrasound-guided fine needle aspiration biopsy found that 5 percent had thyroid cancers, which is the frequency in patients with solitary nodules[17]. In another study, the risk of malignancy was similar in a patient with a single or multiple nodules, but the risk of malignancy was higher in a solitary nodule than in a non-solitary nodule[14]. Thus, a dominant nodule in a multinodular goiter should be evaluated as if it were a single nodule.

Rarely, calcification can occur in these lesions, which can be mistaken for psammoma bodies, especially in fine needle aspirate (FNA) specimens[18].

Multiple encapsulated nodules are usually termed "adenomatoid hyperplasia"[15]. It is evident now that clonal proliferations[15,16], occur in up to 70% of the hyperplastic nodules and can express various markers of malignant follicular derived thyroid tumours such as peroxisome proliferator activated receptor (PPAR) and RET[19]. This may also explain why malignant transformation in follicular patterned lesions of

the thyroid involves a sequence of molecular events originating in adenomatoid hyperplasia and leading to carcinoma. Approximately 15 percent of all differentiated thyroid cancers may behave in an aggressive manner[14]. They can metastasize and, in older patients who present with a cancer that invades through the thyroid capsule, the long-term mortality is 35 to 65 percent. Anaplastic carcinomas, some medullary cancers, and thyroid lymphomas are also associated with higher mortality, but are encountered less commonly than differentiated thyroid cancer[14].

We are of the view that follicular adenoma, and microfollicular adenomatoid nodule is the most common follicular pattern in thyroid gland lesion which should be identified and managed accordingly with the help of careful microscopic examination and immunohistochemistry.

CONCLUSION

We concluded that follicular pattern in thyroid lesions can be due to benign pathology or malignant neoplasm. Microfollicular adenomatoid nodule and follicular adenoma are the frequent thyroid gland lesions presenting with follicular pattern on histopathological examination. In this regard, meticulous microscopic examination and immuno-histochemistry is required for the proper identification of the lesion.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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