ORIGINAL RESEARCH PAPER

Volume-8 | Issue-4 | April-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

DIAGNOSTIC DILEMMAS IN CYTOLOGICAL ASSESSMENT OF THYROID NODULES

Pathology

Dr. Shruti Singh Associate Professor And Head, Department Of Pathology, Government Medical College, Datia

Dr. Poonam Woike* Demonstrator, Department Of Pathology, Government Medical College, Datia *Corresponding Author

Dr. D. Nath Professor And Head, MLB Medical College Jhansi

Dr. Rajesh Gaur Professor And Dean, Government Medical College, Datia

ABSTRACT

Fine Needle Aspiration Cytology (FNAC) of thyroid has been introduced as the most reliable and cost effective method for diagnosing of clinically important thyroid disorders. The aim of our study is to assess various cytomorphological lesions of thyroid gland and diagnostic dilemmas related to them. A total number of 347 cases were included in the study. Only patients which had a solitary or multiple thyroid nodules were selected for FNA. The FNAC results are classified as benign, malignant, suspicious, and unsatisfactory. A total of 347 cases of thyroid swellings were aspirated during the study period. Among the reported cases female outnumbered the male patients and maximum thyroid lesions were in age group 21-40 yrs. Colloid goiter was prevalent among all age groups whereas anaplastic carcinoma was diagnosed in age group >50 yrs. Majority of cases reported on cytology were non neoplastic. Fine needle aspiration cytology is a rapid, inexpensive OPD procedure for pre operative evaluation of patients with thyroid swellings and should be promoted by clinicians as primary modality in the evaluation of thyroid lesions.

KEYWORDS

Fine Needle Aspiration Cytology; Thyroid lesions; dilemmas.

INTRODUCTION AND BRIEF REVIEW OF LITERATURE-

Sampling thyroid by using needles is one of the oldest diagnostic techniques in the medical history known since 936-1013AD as written in the book of Abu al-Qasim [1]. Most of them are benign [Fig. No.1]; only 5-15% are malignant; [2,3] It is a well-accepted, widely used, minimally invasive, cost effective technique with high sensitivity and specificity, [4].

Cystic Lesions

Pitfalls in the evaluation of cystic lesions and hyperplastic nodules frequently cause diagnostic difficulty in our routine practise. Cysts in thyroid are common, and most of them are benign. However, malignant neoplasms may also present as cystic lesions.

A. True Cysts

Thyroglossal duct cysts, parathyroid cysts, epidermoid cysts, branchial cleft cysts can all occur either in thyroid or near thyroid (lateral midline cysts) [5]. The reported rate of parathyroid cysts is 0.6-3%, thyroglossal cysts is 7% including paramidline localization [5-7]. Depending on the sampling track or the nature of the lesion as in thyroglossal duct cyst,follicular epithelium can be observed in their aspirates and cause diagnostic difficulties[7]. Ciliated cells, lymphocytes, squames, colloid, keratin are the components helping in the differential diagnosis[5, 6]. Colorless or water-clear fluid mostly suggest parathyroid cysts, the others as well as thyroid cysts/ pseudocysts are characterized by yellowish to brown cyst contents [5,8]. The biochemical analysis of the cyst fluid has great value in differentiating parathyroid cysts from the others [5,8].

B. Pseudocysts/ Hyperplastic Nodules

Hyperplastic nodules tend to undergo cystic/ degenerative/ reparative changes; haemorrhage, stromal fibrosis, hyalinization, necrosis and calcification may occur [3,9]. Then, the aspirates show foamy cells, hemosiderin-laden macrophages, proteinaceous granular debris/ watery colloid, scarce amount of epithelium and fibroblasts [10-12]. Nuclei can be large, round to oval but always with regular borders, and may show grooves and hypochromasia with distinct nucleoli [10-12]. In a study on thyroid cysts containing atypical cells, among 12 selected cytological features, intranuclear pseudoinclusions, papillary microarchitecture, nuclear crowding and mitoses were the ones suggesting carcinoma [11]. Cytoplasmic characteristics vary from scant to large, mildly vacuolated, plump with thyroglobulin blebs or oncocytic [3,13]. However, focal nuclear atypia including grooves, oval shape, chromatin clearing, and overlapping are reported in hyperplastic nodules causing diagnostic difficulties [14].

C. Malignancies with Cystic Component

Follicular neoplasms; [Fig No.4], PTC and MTC may have cystic components, and aspirates from those cystic tumours usually yield hypocellular specimens causing false negative diagnosis [10-12, 15]. Tumour cells in cyst fluids, especially cells from PTC may show cytoplasmic hypervacuolization and can be misinterpreted as macrophages (histiocytes). [13] Immunohistochemistry and/or serum calcitonin levels will help to solve the diagnostic dilemma in such cases. [15,16]

Graves' disease

Graves' disease is a common cause of hyperthyroidism, and seen in 0.5% of the United States population. Reported rates of malignancy vary between 2.3- 19% [17]. Oncocytic and/ or non-oncocytic thyroid follicular epithelial cells, high amount of flame cells, watery colloid, lymphocytes, and rarely granulomas are seen in aspirations [18]. Cytological findings are challenging, especially after treatment [19]. Distinctive leomorphism, hyperchromasia, elongation of nuclei with occasional grooves and inclusions can be seen in this benign entity. [18-20]

Amyloid goiter

It can be a sign of primary or secondary amyloidosis (amyloid goitre) or can accompany plasmacytomas and MALT lymphomas [21,22]. Presence of amyloid may cause inflammation, reactive changes and giant cell reaction leading to an atypical/suspicious diagnosis. [23-25]

Inflammatory lesions

A. Granulomatous Thyroiditis

Granulomatous reaction due to subacute thyroiditis (De Quervain's thyroiditis); [Fig. no.2,3] is much more common than other granulomatous conditions of thyroid such as fungal infections, tuberculosis or sarcoidosis. [26]. Numerous neutrophils, mononucleated inflammatory cells are seen in early stage while increased amount of fibrous stromal fragments and abundant multinucleated giant cells mixed with lymphocytes are much prominent in late stage. [27,28]

B. Lymphocytic Thyroiditis

Nuclear grooves and even pseudoinclusions are described in Hashimoto's thyroiditis [13,29]. Indeed Hashimoto's thyroiditis is one of the most common causes of false positive PTC diagnosis [3,30-33].

Follicular lesions

The follicular lesions of thyroid basically encompass adenomatous nodule (AN), follicular adenoma (FA), and follicular carcinoma (FC) that can be simply defined by the presence of a capsule (AN vs. FA) and capsular/ vascular invasion (FA vs. FC) on histopathological grounds

(34, 35). FN/SFN is the category covering these lesions in the Bethesda System for Reporting Thyroid Cytology (TBSRTC). [41] Sheets/clusters or microfollicules may dominate in the aspirates; generally many bare nuclei are present in the background; rarely anisokaryosis and occasionally colloid like-parathyroid secretions can be seen[37]. Particularly for the aspirates from thyroidectomy beds which show microfollicular pattern, parathyroid tissue should always be remembered in the differential diagnosis [38]. Naked nuclei in the background are common; microfollicles, may be seen [39,40]

Oncocytic Lesions

Oncocytic lesions of thyroid present a spectrum from hyperplasia / metaplasia to neoplasia that have always attracted pathologists and cytopathologists by their unique cell morphology [41, 42]. In the study of Elliot et al. from 14 designated cytomorphologic features, the following ones endorsed malignancy for oncocytic aspirates; non-macrofollicular architecture, absence of colloid and inflammation, presence of transgressing blood vessels [43]. Background colloid, inflammation and also the ratio of oncocytic cells are important to identify nonneoplastic nodules; the aspirates from oncocytic neoplasms are composed of >70% oncocytes [44].

Papillary Thyroid Carcinoma (PTC)

PTC is the most common thyroid malignancy. According to the SEER (the US Surveillance, Epidemiology and End Results) program between 2002-2011, thyroid cancer has increased more than any other malignancy including cervix uteri, breast, colon and prostate cancer [45]. This trend is mainly explained by the improvement in the diagnostic modalities, widespread use of advanced imaging techniques [46,47]. Among the nuclear features of PTC, the most specific is intranuclear pseudo inclusions however they are not present in all cases [48]. Pseudopapillary formation as an architectural pitfall is well emphasized in the study of Majahan et al. [49,50]. stromal degenerative fragments can mimic bubble-gum type colloid and large amounts of loose colloid may also be seen in PTC [13]. Keeping in mind that all the cytological features cannot be present in each case one should be careful not to miss PTC; on the other hand, not to overdiagnose nuclear and/or pattern atypia in benign entities as PTC [13,51,52].

Medullary thyroid carcinoma (MTC)

True oncocytes display centrally placed nuclei with macronucleoli which are unusual for MTC [13,53]. If totally dispersed cell pattern is seen, could be misinterpreted as lymphoma and plasmocytoma [53]. However, distinguishing these entities by cytomorphology alone is nearly impossible, clinical findings and immunohistochemistry is needed [54]. C cell hyperplasia can also nicely mimic MTC, if c-cell hyperplasia forms nodules large enough to be detected by ultrasonography and successfully aspirated, or in a blind aspiration from a patient with elevated serum calcitonin level, there is no solution to discriminate c-cell hyperplasia from MTC by cytomorphology alone, still should be remembered as a possibility [55].

MATERIALS AND METHODS

Present study is a retrospective study done in the Cytopathology section in coherence with department of surgery and medicine. A total number of 347 cases were included in the study with diffuse/nodular thyroid enlargement. Informed consent was taken from the patients. The records of these patients were retrieved and information about age, sex, cytomorphological diagnosis were recovered were compiled in tabulated form. FNAC in all these patients was performed by experienced cytologists without local/general anaesthesia with 22-23g needle. The procedure was well tolerated by the patients without any complication. Air dried smears were prepared from aspirated material and stained with MGG following recommended steps. Cytological smears were reviewed according to standard guidelines and diagnosis was accordingly classified and correlated with age and sex to explore the pattern and association.

The data was compiled, summarized and analyzed statistically using frequency distribution and percentage proportion.

RESULTS

A total number of 347 cases of thyroid swellings were aspirated during the study period . Among the reported cases female outnumbered the male patients and maximum thyroid lesions were in age group 21-40 yrs. Colloid goiter was prevalent among all age groups whereas anaplastic ca was diagnosed in age group >50 yrs. Cytomorphological lesions were categorized into 4 categories- 1. Inadequate 2.Benign 3. Suspicious 4. Malignant. Majority of cases reported on cytology were non neoplastic . The following tables show the spectrum of various thyroid lesions and male/ female preponderance in our study [table no.1,2,3].

Table No.1. Spectrum of Different Thyroid Lesions.

S.no	Diagnosis	Total no. of cases	Percentage
1.	Colloid goiter	123	35.5
2.	Nodular colloid goiter	90	25.9
3.	Hashimoto's thyroiditis	27	7.8
4.	Lymphocytic thyroiditis	05	1.4
5.	De quervain's thyroiditis	04	1.2
6.	Granulomatous thyroiditis	07	2.0
7.	Grave's disease	08	2.3
8.	Papillary carcinoma	10	2.9
9.	Anaplastic carcinoma	06	1.7
10.	Medullary carcinoma	05	1.4
11.	Colloid cyst	12	3.5
12.	Follicular neoplasm	35	10.1
13.	Follicular adenoma	15	4.3
Total		347	100

Table no. 2 : Age wise distribution of number of cases

S.No	Age Group	No. Of Cases	Percentage
1.	<20 Yrs	67	19.3
2.	21-40 Yrs	156	45
3.	41-60 Yrs	82	23.6
4.	>60 Yrs	42	12.1

Table No.3 Male/ Female Distribution.

S.No	Gender	No. Of Cases	Percentage
1.	Male	79	22.8
2.	Female	268	77.2

DISCUSSION

FNAC was first proposed in 1904 to sample lymph node in sleeping sickness. In 1930 Martin & Ellis described it as a valuable step in the workup of neck lumps included in thyroid nodules[56]. The management of patients with thyroid illness has been drastically changed after the evolution of FNAC. FNAC of thyroid swellings is reported to have sensitivity range of 65-98% & specificity of 70-100%. Cytological categorization of thyroid lesions into benign and malignant is very helpful to clinicians in the management of patients with specific reference to the need of thyroid surgery, as most of the benign conditions can be managed medically. It is useful to remind that there are different classification systems for thyroid FNA reporting. Kumar et al in their study on 89 patients with enlarged thyroid gland reported a sensitivity of 100% & diagnostic accuracy of 97.7% [57]. Our study and other expertise;[58] strongly suggest that FNAC is more specific than sensitive in detecting thyroid malignancy, therefore it should be adapted as a reliable initial diagnostic test in all tertiary hospitals like ours, in developing countries like India. In the published data; [59-61] the sensitivity, specificity and accuracy of thyroid FNAC in detecting malignancy ranges from 52- 86%,52-86.6% and 79.1% respectively.

In present study , among the benign category the most common lesion was found- colloid goiter (35.5%) followed by nodular colloid goiter (25.9%). Thyroiditis included hashimoto's (7.8%) followed by lymphocytic (1.4%) de quervain's; [FIG. NO.2,3] (1.2%) and granulomatous (2.0%) grave's disease was reported in 2.3 % of cases. Follicular neoplasm [FIG. NO.4] were 10.1% and follicular adenoma reported were 4.3% Among the suspicious for malignancy group most cases were given differential diagnosis (D.D) of nodular goiter, D.D follicular neoplasm, D.D hurthle cell neoplasm. Malignant category included papillary carcinoma (2.9%) followed by anaplastic carcinoma (1.7%) & medullary carcinoma (1.4%).

An interpretation of a colloid nodule in which there is abundant, thick colloid present does not require a minimum number of follicle cells [62]. The diagnosis of a benign thyroid lesion should be made only on adequate samples, whereas the presence of atypical cells or cellular pattern, always should be addressed regardless of cellularity and it precludes the interpretation of an inadequate sample.[63]

Cytological differentiation between follicular neoplasm and nodular goiter is often difficult.[64] No reliable cytologic feature distinguish follicular adenoma from follicular carcinoma and distinction between

the two is based solely on demonstration of histologic evidence of capsular/and or vascular invasion.[62] Hence, multiple passes to cover all areas of interest, and USG-guided aspiration reduces sampling error.[65]

Continued surveillance for a nodule with repeat second benign cytology is not needed [66]. Consideration could be given to administration of levothyroxine therapy to keep the TSH in the range of 0.1–1 mU/L [67].

The correlation of cytological and histopathological diagnoses is an important quality assurance method as it allows cytopathologists to calculate their false positive and false negative results. The false negative rate (FNR) is defined as the percentage of cases with benign cytology but proven to be malignant after histopathological examination.

CONCLUSION

Fine needle aspiration cytology is a rapid inexpensive, initial diagnostic test for preoperative evaluation of patients with thyroid swellings. It should be promoted by clinicians as primary modality in the evaluation of thyroid lesions. FNAC is an important adjunct to the careful physical examination and evaluation of patients with thyroid swellings. it is imperative for clinicians, radiologists and pathologists to understand and accept that some thyroid lesions, like some lesions in any other part of the body, defy categorization on FNAC and must be subjected to thorough histopathological evaluation for proper management of the patient.

REFERENCES-

1. Baloch ZW, Bedrossian C. Following the steps of Abu al-Qasim to Bethesda and beyond: The continuing deliberations in thyroid fine-needle aspiration. Diagn Cytopathol. 2012; 40 Suppl1:E1-3.
2. Faquin WC. Diagnosis and reporting of follicular-patterned thyroid lesions by fine needle aspiration. Head Neck Pathol. 2009;3:82-5.
3. B aloch ZW, LiVolsi VA. Current role and value of fine-needle aspiration in nodular goitre. Best Pract Res Clin Endocrinol Metab. 2014; 28:531-44.
4. Cooper DS, et al Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009; 19:1167-214.
5. De May Richard. The Art and science of cytopathology. 2nd ed. Chicago: ASCP;2012.
6. U jiki M, Sturgeon C, Nayar R, Angelos P Parathyroid cyst: Often mistaken for a thyroid cyst. World J Surg. 2008; 32:1234.
7. Wei S, LiVolsi VA, Baloch ZW Pathology of thyroglossal duct: An institutional experience. Endocr Pathol. 2015; 26:75-9.
8. Rossi ED, Revelli L, Giustozzi E, Straccia P, Stigliano E, Lombardi CP, Pontecorvi A, Fadda G Large non-functioning parathyroid cysts: Our institutional experience of a rare entity and a possible pitfall in thyroid cytology. Cytopathology. 2015; 26:114-21.
9. Mete O, Asa SL. Pitfalls in the diagnosis of follicular epithelial proliferations of the thyroid. Adv Anat Pathol. 2012; 19: 363-73.
10. Jaragh M, et al Predictors of malignancy in thyroid fine-needle aspirates "cyst fluid only" cases: Can potential clues of malignancy be identified? Cancer. 2009; 117:305-10.
11. Faquin WC, Cibas ES, Renshaw AA. "Atypical" cells in fineneedle aspiration biopsy specimens of benign thyroid cysts. Cancer. 2005; 105:71-9.
12. Jaffar R, Mohanty SK, Khan A, Fischer AH. Hemosiderin laden macrophages and hemosiderin within follicular cells distinguish benign follicular lesions from follicular neoplasms. Cytojournal. 2009; 6:3.
13. A li SZ, Nayar R, Krane JF, Westra WH. Atlas of Thyroid cytopathology with histopathologic correlations. New York:Demos Medical Publishing;2014.
14. Pusztaszeri MP, Krane JF, Cibas ES, Daniels G, Faquin WC. FNAB of benign thyroid nodules with papillary hyperplasia: A cytological and histological evaluation. Cancer Cytopathol. 2014; 122:666-77.
15. Fadda G, et al Cystic medullary thyroid carcinoma: Report of a case with morphological and clinical correlations. Endocr Pathol 2000;11:373-7.
16. Hyrcza MD, Winer D, Mete O. Images in endocrine pathology: Papillary variant of medullary thyroid carcinoma with cystic change. Endocr Pathol. 2015; 26:87-9.
17. Chen YK, et al Cancer risk in patients with Graves' disease: A nationwide cohort study. Thyroid. 2013; 23:879-84.
18. Anderson SR, et al Can cytomorphology differentiate between benign nodules and tumors arising in Graves' disease? Diagn Cytopathol. 2004;31:64-7.
19. B aloch ZW, LiVolsi VA. Fine-needle aspiration of the thyroid: Today and tomorrow. Best Pract Res Clin Endocrinol Metab. 2008;22:929-39.
20. B rito JP, Gionfriddo M, Morris JC, Montori VM. Overdiagnosis of thyroid cancer and graves' disease. Thyroid. 2014; 24:402-3.
21. Villa F, Dionigi G, Tanda ML, Rovera F, Boni L. Amyloid goiter. Int J Surg. 2008;6 Suppl 1:S16-8.
22. Nobuoka Y, Hirokawa M, Kuma S, Takagi N, Higuchi M, Masuoka H, Miya A, Kubota S, Miyauchi A Cytologic findings and differential diagnoses of primary thyroid MALT lymphoma with striking plasma cell differentiation and amyloid deposition. Diagn Cytopathol. 2014; 42:73-7.
23. Hamed G, Heffess CS, Shmookler BM, Wenig BM. Amyloid goiter. A clinicopathologic study of 14 cases and review of the literature Am J Clin Pathol 1995; 104:306-12.
24. Michael CW, Naylor B. Amyloid in cytologic specimens. Differential diagnosis and diagnostic pitfalls. Acta Cytol. 1999; 43:746-55.
25. O zdemir BH, Uyar P, Ozdemir FN Diagnosing amyloid goiter with thyroid aspiration biopsy. Cytopathology. 2006;262-6.
26. Shabb NS, Salti I Subacute thyroiditis: Fine-needle aspiration cytology of 14 cases presenting with thyroid nodules. DiagnCytopathol. 2006;34:18-23.
27. Nikiforov EY. Diagnostic pathology and molecular genetics of the thyroid. 2nd ed. Philadelphia: Lipincott;2012.
28. Mordes DA, Brachtel EF. Cytopathology of subacute thyroiditis. Diagn Cytopathol. 2012;40:433-4.
29. Harvey AM, Truong LD, Mody DR. Diagnostic pitfalls of Hashimoto's/lymphocytic thyroiditis on fine-needle aspirations and strategies to avoid overdiagnosis. Acta Cytol. 2012; 56:352- 60.
30. Junik R, Juraniec O, Pypkowski J, Krymer A, Marszalek A. A difficult diagnosis: A case report of combined Riedel's disease and fibrosing Hashimoto's thyroiditis. Endokrynol Pol. 2011 62:351-6.
31. Ylagan LR, Farkas T, Dehner LP Fine needle aspiration of the thyroid: A cytohistologic correlation and study of discrepant cases. Thyroid. 2004; 14:35-41.
32. Kollur SM, El Sayed S, El Hag IA. Follicular thyroid lesions coexisting with Hashimoto's thyroiditis: Incidence and possible sources of diagnostic errors. Diagn Cytopathol. 2003; 28:35-8.
33. MacDonald L, Yazdi HM. Fine needle aspiration biopsy of Hashimoto's thyroiditis. Sources of diagnostic error. Acta Cytol. 1999; 43:400-6.
34. B aloch ZW, LiVolsi VA. Follicular-patterned afflictions of the thyroid gland: Reappraisal of the most discussed entity in endocrine pathology. Endocr Pathol. 2014; 25:12-20.
35. B aloch ZW, LiVolsi VA. Our approach to follicular-patterned lesions of the thyroid. J Clin Pathol. 2007; 60: 244-50.
36. The Bethesda System for reporting thyroid cytopathology. Syed AZ, Cibas ES, editors. New York: Springer;2010.
37. A garwal AM, Bentz JS, Hungerford R, Abraham D Parathyroid fine-needle aspiration cytology in the evaluation of parathyroid adenoma: Cytologic findings from 53 patients. Diagn Cytopathol. 2009;37:407-10.
38. Bishop JA, Owens CL, Shum CH, Ali S. Thyroid bed fine-needle aspiration: Experience at a large tertiary care center. Am J ClinPathol. 2010; 134:335-9.
39. Lastra RR, LiVolsi VA, Baloch ZW. Aggressive variants of follicular cell-derived thyroid carcinomas: A cytopathologist's perspective. Cancer Cytopathol. 2014; 122:484-503.
40. Bongiovanni M, et al Cytomorphologic features of poorly differentiated thyroid carcinoma: A multi-institutional analysis of 40 cases. Cancer. 2009; 117:185-94.
41. A sa SL My approach to oncocytic tumours of the thyroid. J ClinPathol. 2004;57:225-32.
42. Maximo V, Rios E, Sobrinho-Simoes M. Oncocytic lesions of the thyroid, kidney, salivary glands, adrenal cortex, and parathyroid glands. Int J Surg Pathol. 2014; 22:33-6.
43. E lliott DD, Pitman MB, Bloom L, Faquin W. Fine-needle aspiration biopsy of Hurthle cell lesions of the thyroid gland: A cytomorphologic study of 139 cases with statistical analysis. Cancer. 2006; 108:102-9.
44. Montone KT, Baloch ZW, LiVolsi VA. The thyroid Hürthle (oncocytic) cell and its associated pathologic conditions: A surgical pathology and cytopathology review. Arch Pathol Lab Med. 2008;132:1241-50.
45. Ito Y, Nikiforov YE, Schlumberger M, Vigneri R. Increasing incidence of thyroid cancer: Controversies explored. Nat RevEndocrinol. 2013; 9:178-84.
46. Vigneri R, Malandrino P, Vigneri P The changing epidemiology of thyroid cancer: Why is incidence increasing? Curr Opin Oncol.2015; 27:1-7.
47. Tufano RP, Noureldine SI, Angelos P. Incidental thyroid nodules and thyroid cancer: Considerations before determining management. AMA Otolaryngol Head Neck Surg. 2015;141:566-72.
48. Das DK, Sharma PN. Diagnosis of papillary thyroid carcinoma in fine needle aspiration smears: Factors that affect decision making. Acta Cytol. 2009; 53:497-506.
49. Mahajan A, Lin X, Nayar R. Thyroid Bethesda reporting category, 'suspicious for papillary thyroid carcinoma', pitfalls and clues to optimize the use of this category. Cytopathology. 2013; 24:85-91.
50. Khayyata S, Barroeta JE, LiVolsi VA, Baloch ZW. Papillary hyperplastic nodule: Pitfall in the cytopathologic diagnosis of papillary thyroid carcinoma. Endocr Pract. 2008; 14: 863-8.
51. Nassar A, Gupta P, LiVolsi VA, Baloch Z Histiocytic aggregates in benign nodular goiters mimicking cytologic features of papillary thyroid carcinoma (PTC). Diagn Cytopathol. 2003;29:243-5.
52. Renshaw AA Fine-needle aspirations of papillary carcinoma with oncocytic features: An expanded cytologic and histologic profile. Cancer Cytopathol. 2011; 119:247-53.
53. Chetty R. Hurthle cell medullary carcinomas of the thyroid gland. S Afr J Surg. 1990; 28:95-7.
54. Sivrikoz E, et al Neuroendocrine tumors presenting with thyroid gland metastasis: A case series. J Med Case Rep. 2012;6:73.
55. A ulicino MR, et al Cytologic findings in the differential diagnosis of C-cell hyperplasia and medullary carcinoma by fine needle aspiration. A case report Acta Cytol. 1998;42:963-7.
56. Guhamallick et al. cytodignosis of thyroidusefulness & pitfalls: a study of 288 cases. J cytol2008;25:6-9
57. Kumar S. aquil et al. role of FNAC in thyroid diseases . j surg.Pk2008;13:22-5.
58. Bukhari MH et al. an update audit of fine needle aspiration cytology procedure of solitary thyroid nodule. Diagncytopathology2008;36:104-12.
59. Giuseppe A, Maria P, Italo N. Fine needle aspiration cytology of thyroid gland disease. The International Academy of cytology; March-April, 1990, vol 34, No.2.
60. Cap J, Rehorkova P, Hovorkova E, Kerekes Z, Pohnetelova D. Sensitivity and specificity of fine needle aspiration biopsy of thyroid gland: clinical point of view. Clinical endocrinology, 1999, 51: 509- 515p.
61. Holleman F, Hoekstra J, Ruitenberg HM. Evaluation of fine needle aspiration cytology in the diagnosis of thyroid nodules. Cytopathology. 1995; 6: 175-186.
62. Guidelines of the Papanicolaou Society of Cytopathology for fine-needle aspiration procedure and reporting. The papanicolaou society of cytopathology task force on standards of practice. Diagn Cytopathol. 1997;17:239–47. [PubMed]
63. Yang J, Schnadig V, Logrono R, Wasserman PG. Fine-needle aspiration of thyroid nodules: A study of 4703 patients with histologic and clinical correlations. Cancer. 2007;111:306–15. [PubMed]
64. Orell SR, Sterrett GF, Whitaker D. Fine Needle Aspiration Cytology. 4th ed. Philadelphia: Churchill Livingstone; 2005. Thyroid; pp. 125–64.
65. Baloch ZW, Tam D, Langer J, Mandel S, LiVolsi VA, Gupta PK. Ultrasound-guided fine-needle aspiration biopsy of the thyroid: Role of on-site assessment and multiple cytologic preparations. Diagn Cytopathol. 2000;23:425–9.
66. Durante C, Costante G, Lucisano G, et al. The natural history of benign thyroid nodules. Jama. 2015;313(9):926–935. doi: 10.1001/jama.2015.0956.
67. Messuti I, Corvisieri S, Bardesono F, et al. Impact of pregnancy on prognosis of differentiated thyroid cancer: clinical and molecular features. Eur J Endocrinol. 2014;170(5):659–666. doi: 10.1530/EJE-13-0903.