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Aspiration cytology of Hashimoto's thyroiditis in an endemic area

NEETA KUMAR, CHETAN RAY AND SHYAMA JAIN
Cytopathology Unit, Department of Pathology, Maulana Azad Medical College and LN Hospital, New Delhi 110001, India

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Fine needle aspiration (FNA) plays a significant role in the diagnosis of thyroid lesions due to its simplicity and low cost. Hashimoto's thyroiditis (HT) is the second most common thyroid lesion next to endemic goitre diagnosed on FNA in iodine (I_2) deficient areas. Data on its incidence, prevalence and clinicopathological features in I_2 deficient areas is scanty compared to I_2 sufficient areas. In the present study the patients presented with HT a decade earlier than reported in I_2 sufficient areas. Presentation as a nodular thyroid is common. Diagnosis of HT is likely to be missed in smears showing cytological evidence of hyperplasia or abundant colloid. HT was concurrent in 20 cases of endemic goitre. Careful screening for Hurthle cell change and lymphocytic infiltration into follicular cells should be carried out. In equivocal cases multiple punctures and immunological investigations are helpful. In antibody-negative cases repeat FNA at follow-up is useful. Marked lymphocytic infiltration and Hurthle cell change may indicate a hypothyroid state but hormonal levels are required for clinical management.

Keywords: Hashimoto's thyroiditis, fine needle aspiration cytology, hyperplasia, endemic goitre

INTRODUCTION

Hashimoto's thyroiditis (HT) is common in iodine (I_2) sufficient areas, with a prevalence rate of 1–4% and incidence of 3–6/10 000 population per year.[1] The prevalence of HT in I_2 deficient regions in India before I_2 supplementation varied from 5–14% as assessed on core biopsy and thyroidectomy specimens.[2–3] Delhi is a known endemic region for I_2 deficiency and has been under I_2 supplementation since 1989.[4] A high prevalence (13.8%) of chronic lymphocytic thyroiditis (CLT) in goiterous adolescent females in Delhi was reported nine years after I_2 supplementation.[5] In our experience HT is the second most

Correspondence: Neeta Kumar, 178 Hauz Khas Apartments (SFS), New Delhi 110016, India.

common thyroid lesion next to goitre diagnosed on fine needle aspiration (FNA). FNA is the method of choice for initial diagnosis of all thyroid lesions in developing countries where access to hormonal assays, antibody testing and sophisticated radiological scanning is difficult. The major problem in I_2 deficient areas is differentiating HT from endemic goitre clinically and cytologically, as the incidence of thyroid neoplasms is very low.

This paper describes the clinico-cytomorphological spectrum of HT and its correlation with hormonal and antibody status. Coexistence with endemic goitre and diagnostic pitfalls in endemic areas under I_2 supplementation are highlighted.

MATERIALS AND METHODS

A total of 608 thyroid lesions underwent FNA during the study period (1997–98). The cytological diagnosis of HT was suggested in 86 cases. In 55 of these, levels of thyroid hormones and antibody status were available from our hospital records and formed the basis of this study. T_3, T_4 and TSH levels in blood were estimated by radioimmunoassay. Antimicrosomal (AM) antibody levels were measured using indirect agglutination kits (Fuji Re Bio Inc., Japan). A titre of 1:1600 or more was regarded as significant.

FNA was done with a 23-guage needle. Smears were air-dried and stained by the Giemsa method. Detailed cytological features were noted. Hurthle cells and lymphocytic infiltration into epithelial groups were graded in a semi-quantitative manner as low and heavy, and correlated with hormonal and antibody status. To test the association of cytological diagnosis with hormonal and antibody status, either a chi-square test of significance or Fischer exact test was employed.

RESULTS

All 55 patients were females ranging in age from 7 to 45 years (mean = 14). Forty-one patients (74.5%) were below 30 years. Forty-five patients (81.8%) presented with diffuse, mild to moderate thyroid enlargement while 10 (18.2%) had a single nodule varying from 2 to 4 cm in the largest diameter. The swellings were firm and non-tender. Clinically 28 patients (66.6%) had functional disturbances. Hormonal assay detected 39 patients (72%) with deranged levels.

Table 1 shows the spectrum of cytological diagnosis and its correlation with functional and antibody status. Group I consisted of 35 cases showing a combination of follicular cells, Hurthle cells and lymphocytes in the background, as well as lymphocytic infiltration of epithelium; this group was diagnosed as 'HT' (Figure 1). 20% of these were negative for AM antibody. Follicular cells were seen in honeycomb sheets, microfollicular and syncytial patterns. Hurthle cells in sheets and small clusters showed mild to moderate pleomorphism. Eight cases of 'HT with colloid goitre' (Group II) showed abundant colloid along with classic features of HT (Figure 2). All were antibody positive. In 12 cases, the possibility of 'HT/CLT along with hyperplastic goitre' (Group III) was suggested due to a prominent syncytial and microfollicular pattern, fire flare activity, focal Hurthle cell change, moderate colloid and lymphocytes in the background (Figures 3a,b). Lymphocytic infiltration of epithelial groups was not seen, although 10 cases were antibody positive and eight had hyperthyroidism. Follow up FNA in six of these (including two antibody negative cases) showed a few lymphocytes within epithelium and follicular destruction by lymphoid infiltrate (Figures 3c,d). Overall

Table 1. Cytological diagnosis, hormonal and antibody status

Groups	Cytodiagnosis	Cases (no.)	Hormonal status			Antibody status	
			Euthyroid	Hypo	Hyper	+ve	−ve
Group I	HT	35	11 (31.4)	12 (34.2)	12 (34.2)	28 (80)	7
Group II	HT with colloid goitre	8	3 (37.5)	2 (25)	3 (37.5)	8 (100)	0
Group III	HT/CLT with hyperplastic goitre	12	2 (16.6)	2 (16.6)	8 (66.8)	10 (83.3)	2
	Total	55	16	16	23	46 (83.6)	9

Figures in parentheses indicate percentages.
HT – Hashimoto's thyroiditis.
CLT – chronic lymphocytic thyroiditis.
Hypo – hypothyroidism.
Hyper – hyperthyroidism.

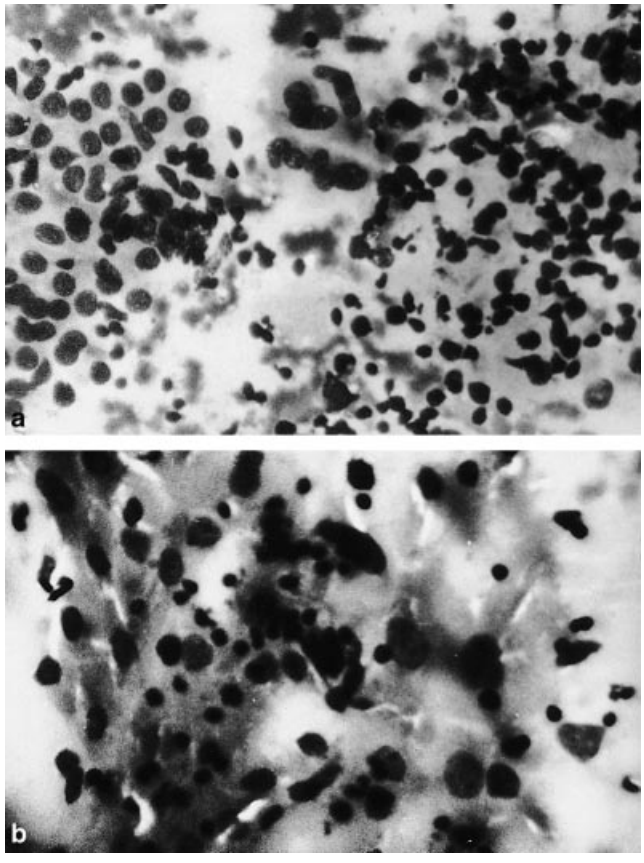

Figure 1. Group I (classical HT). (a) follicular cells, epithelioid cell granuloma and lymphocytic infiltration (Giemsa stain, × 250); (b) lymphocytes infiltrating Hurthle cell cluster (Giemsa stain, × 400).

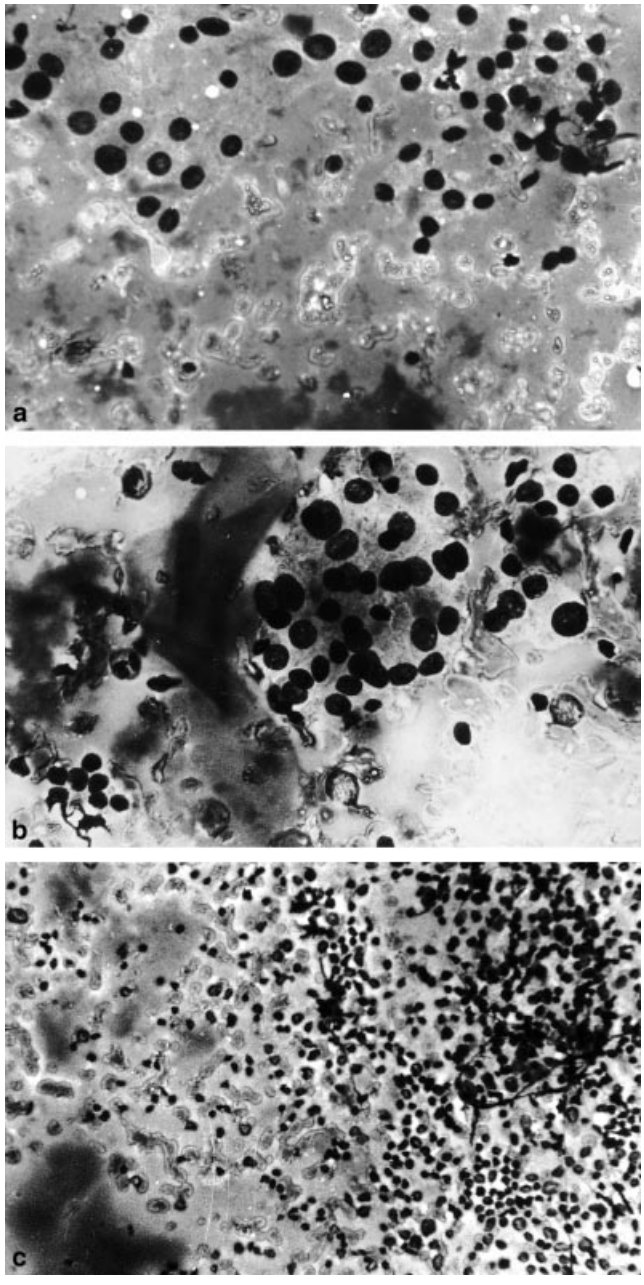

Figure 2. Group II (HT with colloid goitre). (a) follicular cells with abundant thick and thin colloid suggestive of colloid goitre (Giemsa stain, × 400); (b) a few lymphocytes within follicular epithelium, occasional transformed lymphocyte and colloid in the background (Giemsa stain, × 400); (c) another smear from above case showing dense lymphoid infiltrate and abundant colloid (Giemsa stain, × 250); (d) epithelioid cell granuloma and lymphoid aggregate in colloid rich background (Giemsa stain, × 400).

antibody positivity was 83.6% (46 cases). On chi–square test the association of hormonal and antibody status with the cytological diagnosis was not statistically significant ($\chi^2 = 4.9,\ P = 0.38;\ \chi^2 = 1.90,\ P = 0.39$).

Other cytological features included foamy macrophages, multinucleated giant cells (17), epithelioid granulomas (15), and colloid, which was abundant (8), moderate (31), or scanty (16 cases). Lymphocytic infiltration within the epithelial groups was seen in 42 (76.3%)

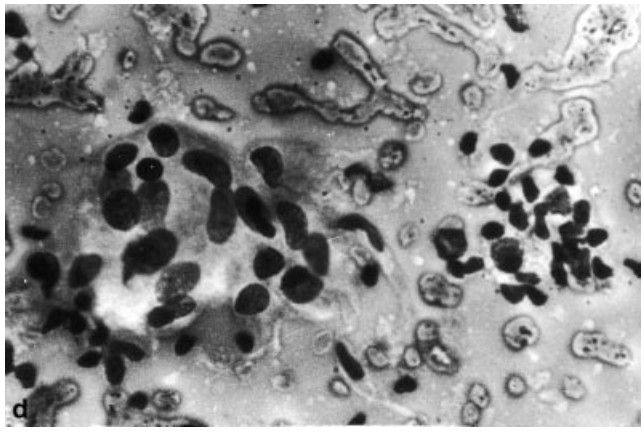

Figure 2. Continued.

cases. Its grading and correlation with functional and antibody status is shown in Table 2. No significant association was found between antibody status and grade of lymphocytic infiltration ($P = 0.24$). The association between hormonal status and lymphocytic infiltration was statistically significant ($\chi^2 = 7.42$, $P = 0.02$). Among 16 cases with moderate to heavy infiltration, the ratio of hypothyroidism (44%) was greater than hyperthyroidism (6%), but no statistically significant association was noted for hypo- or euthyroidism ($\chi^2 = 0.85$, $P = 0.36$; $\chi^2 = 1.13$, $P = 0.29$). Among cases with minimal infiltration the proportion of hyperthyroid cases was greatest (47%) and statistically significant ($P = 0.0006$).

No significant correlation of Hurthle cell population with antibody status ($P = 0.57$) was observed in Table 3. Among 17 cases with a high Hurthle cell population the proportion of hypothyroid patients (59%) was highest. This association was highly significant ($\chi^2 = 8.56$, $P = 0.003$). The association with hyperthyroidism vs. hypo- and euthyroidism was of borderline significance ($P = 0.060$).

DISCUSSION

HT affects females in the fourth decade and above in non-endemic areas.[1] It is noteworthy that two-thirds of our patients were below 30 years of age. A previous study from our centre prior to I_2 supplementation reported an age range similar to that of non-endemic areas.[6] HT presenting as a solitary nodule is considered rare.[7] In our study 18.2% and in another study[8] from India 24% of patients had a nodular presentation. However, no systematic population screening or registry data is available on Indian patients before and after I_2 supplementation.

Clinicoradiological and hormonal parameters overlap in HT and other thyroid lesions, and thus are not very helpful.[6] Seropositivity (83.6%) for AM antibody in our series is consistent with previous studies.[9] Negative serology in 16.4% cases showing cytological evidence of HT can cause a diagnostic dilemma, but it is known that intrathyroidal immune destruction occurs much earlier than serological evidence of antibody.[10]

Cytological features of HT include a mixed population of follicular and Hurthle cells, low to moderate colloid and lymphocytic infiltration of epithelial cell clusters.[6,9,11] Difficulty in distinguishing HT from follicular and Hurthle cell neoplasm has been

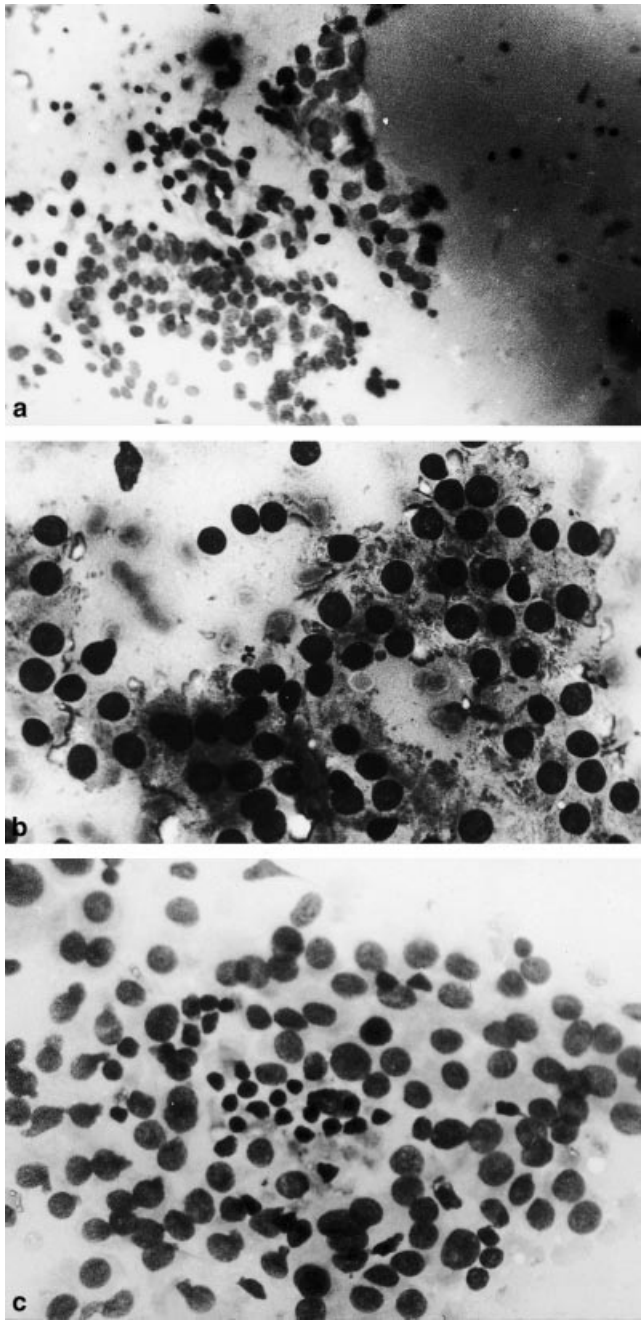

Figure 3. Group III (HT with hyperplastic goitre). (a) syncytial and microfollicular cell pattern, focal Hurthle cell change and moderate colloid (Giemsa stain, × 250); (b) follicular cells showing prominent fire flare (Giemsa stain, × 400); (c) lymphocytic infiltration in the centre of follicular cell cluster (Giemsa stain, × 400); (d) a repeat FNA smear from the above case: follicular cell destruction with heavy infiltration by reactive lymphoid cells (Giemsa stain, × 400).

emphasised in studies from non-endemic areas.[11] In I_2 deficient regions, the incidence of follicular neoplasm being low, adenomatous/colloid/hyperplastic goitre appears to be the main differential diagnosis. In our study smears showing hyperplastic follicular cells, Hurthle cells, a limited population of lymphocytes in the background but absence of

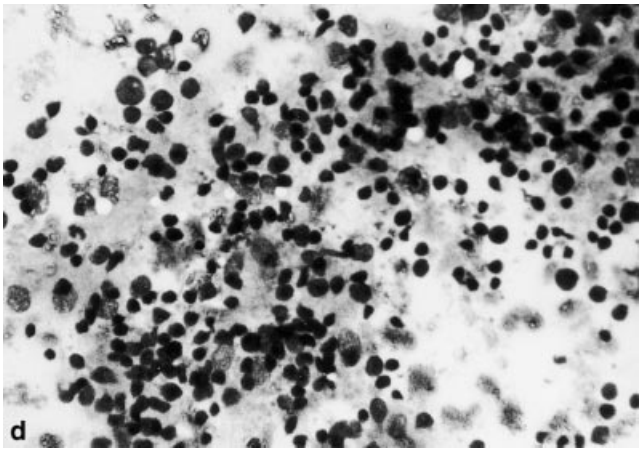

Figure 3. Continued.

Table 2. Correlation of lymphocytic infiltration with hormonal and antibody status

Grades of lymphocytic infiltration	Cases (no.)	Hormonal status			Antibody status	
		Euthyroid	Hypo	Hyper	+ ve	− ve
Minimal	26	8 (30)	6 (23)	**12 (47)**	23 (88.4)	3
Moderate to heavy (+ + to + + +)	16	8 (50)	**7 (44)**	1 (6)	12 (75)	4
Total	42	16	13	13	35	7

Figures in parentheses indicate percentages.
Hypo – hypothyroidism.
Hyper – hyperthyroidism.

Table 3. Correlation of Hurthle cell population with functional and antibody status

Hurthle cells	Cases (no.)	Hormonal status			Antibody status	
		Euthyroid	Hypo	Hyper	+ ve	– ve
Low (± to +)	38	13 (34)	6 (16)	**19 (50)**	32 (84.2)	6
High (+ + to + + +)	17	3 (17)	**10 (59)**	4 (24)	14 (82.3)	3

Figures in parentheses indicate percentages.
Hypo – hypothyroidism.
Hyper – hyperthyroidism.

lymphocytes in epithelial groups posed a major diagnostic problem. A minimal lymphoid population in the background can be seen in endemic goitre. Follow up FNA in six of these cases showed the characteristic feature of lymphocytic infiltration in epithelium (Figure 3c,d). This was helpful in resolving diagnostic uncertainty. In equivocal cases antibody testing is helpful; but if negative, repeat FNA on follow up becomes the ideal choice, especially in early or evolving cases. The possibility of co-existence of these lesions has not been adequately emphasised earlier, but was a

frequent finding in our study. We noticed moderate to abundant colloid in 71% of cases, which is higher than 31% of the cases reported earlier.[12] Abundant colloid may mask lymphocytic infiltration and HT may remain undiagnosed if the cytopathologist is not careful to search for lymphocytes infiltrating epithelial groups, and to eliminate sampling error by multiple punctures.

A higher degree of lymphocytic infiltration and Hurthle cell change signifying marked follicular destruction may indicate a hypothyroid state,[13] as also observed in our study. However cytomorphological features may not always accurately reflect functional status, especially hyper- and euthyroid states. Laboratory assessment of hormonal levels for management and follow up is mandatory.

CONCLUSION

To conclude, the younger age at presentation in our series needs to be investigated by systematic epidemiological studies in the context of I_2 supplementation in endemic areas. A nodular presentation is common in endemic areas. HT can also be seen in association with all types of endemic goitres (adenomatous, colloid and hyperplastic). Diagnosis may be missed in the presence of abundant colloid and hyperplastic follicular cells. The presence of lymphoid cells in the background can lead to over-diagnosis and needs cautious interpretation. Adequate sampling and careful screening of smears for the presence of lymphocytes in epithelial groups and Hurthle cell change is needed for cytological distinction of HT from endemic goitre. If in doubt, FNA from multiple sites on follow up and antibody testing resolve the diagnostic dilemma. In a proper clinical setting the diagnosis of HT may be considered on cytological evidence alone even if AM antibody is negative. This has an added advantage if antibody testing is not possible due to lack of facilities or high cost.

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